Diagnosis and prognosis in connective tissue disease associated pulmonary hypertension

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MD (Research) Thesis

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Authorship Statement

I, Benjamin Emmanuel Schreiber, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: _____

Abstract

The thesis addresses questions of diagnosis and prognosis in connective tissue disease associated hypertension, as addressed in analyses of clinical data from our patients over the last 15 years.

Chapter 1 explores use of pulmonary function tests to improve the detection of patients at risk of pulmonary hypertension. A novel formula is derived and validated.

Chapter 2 evaluates whether the formula described in the previous chapter can be combined with echocardiography and other measures in order to further improve the selection of patients for right heart catheterisation.

In chapter 3 we turn to the prognostic value of 'borderline pulmonary hypertension', exploring indicators of future progression to pulmonary hypertension with important implications for patient care.

In chapter 4 we scrutinise our data on body size and inspected the relationship between obesity and pulmonary hypertension, finding intriguing associations which have not been reported before in this population.

Chapter 5 addresses the very rare diagnosis of lupus associated pulmonary hypertension and compares this small group of patients to scleroderma patients with pulmonary hypertension in order to consider whether their response to treatment and prognosis are distinct.

For chapter 6 we review the relationship between cross-sectional imaging and pulmonary haemodynamics, and specifically address CT findings suggestive of the rare pulmonary veno-occlusive disease.

In chapter 7 we turn our attention to the unfortunate group of patients with systemic sclerosis who develop interstitial lung disease and pulmonary hypertension. We compare their survival to those patients who have pulmonary hypertension without interstitial lung disease and find that lower Kco is most closely associated with poor outcome.

In chapter 8 we review our cohort of patients with systemic sclerosis and pulmonary hypertension and consider whether pulmonary function tests can be combined with pulmonary haemodynamic measures to improve prognostication.

Work in this thesis has been included in the following publications:

Schreiber, B. E., Valerio, C., Handler, C., Keir, G., Lee, R., Martin, R., . . . Coghlan, G. (2011). Diagnosis and Prognosis of Pulmonary Arterial Hypertension in SLE and SSC. *Rheumatology*, 50, 40. Oxford Univ Press.

Schreiber, B. E., Valerio, C., Keir, G., Handler, C., Wells, A. U., Denton, C. P., & Coghlan, J. G. (2011). Diffusion of Carbon Monoxide Predicts Survival in Systemic Sclerosis Patients with Pulmonary Hypertension and Interstitial Lung Disease. Arthritis Rheum, 63 (10), S968.

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Schreiber, B. E., Keir, G., Dobarro, D., Handler, C., Nihtyanova, S., Suntharaligam, J., . . . Coghlan, J. G. (2012). Systemic Sclerosis Associated Pulmonary Hypertension - Is Pulmonary Veno-Occlusive Disease As Common As They Say?. Arthritis Rheum, 64 (10), S310.

Coghlan JG, Schreiber B. An update on the evaluation and management of pulmonary hypertension in scleroderma. Curr Rheumatol Rep. 2012 Feb;14(1):1-10.

Schreiber BE, Connolly MJ, Coghlan JG. Pulmonary hypertension in systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2013 Jun;27(3):425-34.

Valerio, C. J., Schreiber, B. E., Handler, C. E., Denton, C. P., & Coghlan, J. G. (2013). Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. Arthritis Rheum, 65 (4), 1074-1084.

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Preface

Systemic sclerosis (SSc) is a rare, deadly disease which can cause catastrophic complications, especially interstitial lung disease[1] and pulmonary hypertension.[2] This research has been performed since January 2010 as part of my academic and clinical roles within the scleroderma and pulmonary hypertension services at the Royal Free Hospital, initially as a clinical research fellow and then as a consultant physician.

I set out to analyse our large experience over the last 15 years in order to improve clinical management of these rare and very serious conditions. The sequence of the chapters follows a typical patient's path, with chapters 1-4 focusing on diagnosis of pulmonary hypertension, chapters 5-6 with clinical course of the disease and unusual presentations, and chapters 7-8 with natural history and prognosis.

In chapter 1 I explore whether pulmonary function tests can be used to improve the detection of patients at risk of pulmonary hypertension. In this chapter I generated a formula to predict the mean pulmonary artery pressure based on a combination of oxygen saturation and measurement of diffusion of carbon monoxide. This formula was then generated and validated in separate patient groups within our cohort.

Then in chapter 2 I consider whether the formula described in the previous chapter can be combined with echocardiography and other measures in order to further improve the selection of patients for right heart catheterisation.

In chapter 3 we explore the significance of the pulmonary haemodynamic measurements in patients in whom right heart catheterisation does not find pulmonary hypertension. Can we identify indicators of future progression to pulmonary hypertension? Are there important indicators associated with future progression within the haemodynamic data collected? We found that there are, and these findings may have important implications for patient care.

In chapter 4 we scrutinise our data on body size and inspected the relationship between obesity and pulmonary hypertension. We found intriguing associations which have not been reported before in this population.

In chapter 5 we address the very rare diagnosis of lupus associated pulmonary hypertension and compare this small group of patients to scleroderma patients with pulmonary hypertension in order to consider whether their response to treatment and prognosis are distinct.

For chapter 6 we reviewed CT scans performed near the time of the patient's right heart catheter in order to test the relationship between cross-sectional image findings and pulmonary haemodynamics. We explore here the significance of CT findings suggestive of the rare pulmonary veno-occlusive disease. We find less pulmonary veno-occlusive disease in this patient group than has recently been described.

In chapter 7 we turn our attention to the unfortunate group of patients with systemic sclerosis who develop interstitial lung disease and pulmonary hypertension. We compare their survival to those patients who have pulmonary hypertension without interstitial lung disease. We find that Kco is an important prognostic indicator in this cohort.

In chapter 8 we review our cohort of patients with systemic sclerosis and pulmonary hypertension and consider whether pulmonary function tests can be combined with pulmonary haemodynamic measures to improve prognostication. We find that they can.

I have learnt a huge amount in performing these analyses, and I hope I have managed to shed a little light here and there on areas of these rare diseases.

I would like to acknowledge the tremendous support that I have received while doing this work. It would not have been possible without the continuing personal and professional support and encouragement of Professor Chris Denton and Dr Gerry Coghlan. I am very grateful to them that they offered me a Consultant post at the Royal Free and took it on trust that I would see this

M.D. through to its completion, (although of course the research continues in several different directions).

I would like to thank all the staff of the Rheumatology and Pulmonary Hypertension departments at the Royal Free. I feel deeply indebted to Professor Athol Wells at the Royal Brompton Hospital, who besides being a crucial collaborator on several of the studies performed here and a world-respected colleague, helped me personally by sharing his passion for medical statistics and clinical research and introducing me to STATA.

I would like to thank the Raynaud's and Scleroderma Association for funding some of my ongoing research.

Finally, I owe a debt of gratitude to my wife, Leah, my children and the Almighty.

Introduction

Systemic sclerosis is a multisystem disorder of unknown aetiology which may have several presentations. The current classification was introduced in 1988[3] and expanded in 2001.[4] Classification is based on the amount of skin involvement. If skin involvement is limited to face and distally to elbows and knees, the disease is classified as limited cutaneous systemic sclerosis (LcSSc). If skin involvement is more extensive it is classified as diffuse cutaneous systemic sclerosis (DcSSc). Rarely, a diagnosis can be made in the absence of skin involvement (scleroderma sine scleroderma). The previously described Calcifications, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia (CREST) syndrome is no longer felt to be a useful diagnostic category, as patients with either LcSSc or DcSSc may have these clinical features.[5]

LcSSc is characterised by Raynaud's phenomenon, which usually precedes other symptoms by several years. The Raynaud's phenomenon may be severe and may cause digital ulcers or necrosis. It is associated with anti-nuclear antibodies which stain in an anti-centromere pattern in about 38% of patients.[6] Capillaroscopy usually reveals tortuous, dilated capillaries, which may help to distinguish these patients from the much more common primary Raynaud's phenomenon. Skin thickening usually begins on the fingers (sclerodactyly) and around the mouth and nose.

DcSSc, on the other hand, has a more sudden and progressive onset. There is much more extensive disease and more rapid progression. It is associated with anti-topoisomerase-1 (also known as anti-Scleroderma-70) in about a third.6 Most internal organ complications are more common in patients with diffuse disease, and these tend to occur in the first three years. After that, major organ complications are less likely and skin often improves.

Interstitial lung disease occurs in about 38% of DcSSc and 16% of LcSSC within 5 years after the first non-Raynaud's symptoms of Scleroderma.[7] Two randomised controlled trials suggest

immunosuppression with cyclophosphamide may have a role in treatment of scleroderma associated interstitial lung disease, although the benefits were limited.[8]

Renal crisis occurs in about 15% of DcSSc, and 5% of LcSSc, and is characterised by an abrupt onset of renal failure and severe hypertension. About 25% of patients require dialysis.[9]

Patients frequently suffer with gastrointestinal manifestations. Upper GI involvement leads to dysphagia and reflux and, in severe cases, early satiety and post-prandial vomiting. Bacterial overgrowth frequently leads to chronic diarrhoea. Colonic dysmotility may cause constipation. And the anal sphincter is often affected leading to faecal incontinence.[10]

There is some evidence that annual internal organ assessments with lung function tests, echocardiography and renal function tests are associated with increased survival.7

Pulmonary hypertension is seen at least 8% of systemic sclerosis patients, whether limited or diffuse.2 It may be difficult to recognise in patients with systemic sclerosis because dyspnoea may be caused by many other causes, including anaemia, deconditioning, interstitial lung disease, left ventricular diastolic dysfunction among others.[11]

Currently, the diagnosis of pulmonary hypertension can only be established by cardiac catheterisation. This test is expensive, invasive and associated with some risk, there is a concerted international effort to improve on patient selection for the test, in an attempt to balance the need for early diagnosis of pulmonary hypertension with minimising the number of unnecessary tests.

Although there are now three classes of licensed therapies, survival in systemic sclerosis associated pulmonary hypertension remains poor, with a median 3 year survival of only 52% in a recent systematic review.[12]

In the following chapters we explore issues relating to pulmonary hypertension in systemic sclerosis, with an emphasis on interrogating our retrospective data to find clues to improve diagnosis and to aid in prognostication in this rare but life shortening disease.

Chapter 1. Improving the detection of pulmonary hypertension in systemic sclerosis using pulmonary function tests

E-presentation *at Annual Scientific Meeting of the European Respiratory Society, Barcelona, September 2010*

Schreiber BE, Valerio CJ, Keir GJ, Handler C, Wells AU, Denton CP, Coghlan JG. Improving the detection of pulmonary hypertension in systemic sclerosis using pulmonary function tests. Arthritis Rheum. 2011 Nov;63(11):3531-9.

Winner of Hench Award, ACR 2013

Abstract

Objectives

To construct a readily applicable formula for selecting patients with systemic sclerosis for right heart catheterisation based on pulmonary function tests.

Methods

The diagnostic value of pulmonary function test variables was quantified in 386 patients with systemic sclerosis against right heart catheter data.

Results

We derived the following formula in 257 patients:

Predicted mean pulmonary artery pressure = 136 – SpO_2 – 0.25 x DL_{CO}% predicted

We validated the formula in 129 other patients. The area under the curve is 0.74 (95% CI 0.65,0.83). Using a predicted threshold of 25 mmHg, sensitivity is 93.8% (95% CI 86.2,98) and specificity is 25% (95% CI 13.6,39.6).

When used as a screening procedure in a typical scleroderma population it is projected that patients with predicted mean pulmonary artery pressure below 25 mmHg are unlikely to have pulmonary hypertension (prevalence 4.4%), those with predicted pulmonary artery pressures between 25 to 35 mmHg are at average risk (prevalence of 11%) and those with formula predicted mean pulmonary artery pressures above 35 mmHg are likely to have pulmonary hypertension (prevalence of 69%), justifying right heart catheterization.

In patients with equivocal echocardiography a high formula predicted pressure is strongly associated with the presence of pulmonary hypertension.

Conclusions

We have derived and validated an easily applicable pulmonary function formula for patients with systemic sclerosis which identifies sub-groups with low, average and high prevalence of pulmonary hypertension. It provides information which is complementary to echocardiography and which should improve selection of patients for right heart catheterization.

Introduction

Pulmonary hypertension occurs in up to 12% of patients with systemic sclerosis (SSc).[13] Early identification and treatment of pulmonary hypertension (PH) is important, and may improve survival.7 Although right heart catheterisation (RHC) remains the gold standard test for diagnosing PH, it is invasive and is not ideal as a screening test. Pulmonary function tests (PFT) are recommended as part of annual screening tests in SSc. However, it is not clear which patients require RHC based on PFT findings.

In this study we explore the utility of pulmonary function tests and oxygen saturation in detecting PH in a large cohort of patients with SSc who have undergone RHC. We sought to develop a formula based on oxygen saturation and PFTs which would be of help to select which patients require RHC. In order to derive and validate the formula we split our sample into separate derivation and validation cohorts. We compared our formula to other pulmonary function test based formulae. We then assessed the diagnostic use of our formula in patients with contemporary echocardiography to examine whether pulmonary function tests provide information which is complementary to echocardiography and whether it may help decision making in patients with equivocal echocardiographic findings. Finally, we tested the formula in a cohort of patients with other connective tissue diseases associated with pulmonary hypertension. The information is derived from a large 'real life' clinical cohort and results should be readily applicable to scleroderma cohorts elsewhere.

Patients and Methods

Patients

This study utilized the large cohort of SSc cases that underwent a diagnostic RHC study in our centre. Of the 838 patients with SSc 50 had additional features of overlap connective tissue disease (SLE in 23 patients, myositis in 15 patients, rheumatoid arthritis in 9 patients, Sjogrens syndrome in 7 patients, vasculitis in 1 patient and antiphospholipid syndrome in 1 patient). Patients with SSc overlap syndromes were included. Patients were classified as limited

cutaneous or diffuse cutaneous subset according to the criteria described by LeRoy et al.3 Of these 838 patients, 386 patients had complete PFTs (FVC % predicted, DL_{CO}% predicted and K_{CO}% predicted) within six months of the RHC and SpO_2 at the time of RHC and were included in the study. Patients with incomplete PFT data were excluded. There were no other exclusion criteria. Patients in the study cohort (n=386) were a little younger and more frequently male than excluded patients (n=452) but mean pulmonary artery pressures and mean oxygen saturation were similar. Excluded patients did not differ significantly from the study cohort in RHC data or oxygen saturation.

Investigations were performed as part of routine clinical care. Catheterisation was performed in scleroderma patients with echocardiographic tricuspid jet velocity >3.2 metres/second, in patients with tricuspid jet velocity between 2.8 and 3.2 if there was any clinical suspicion of pulmonary hypertension and in patients with tricuspid jet velocity below 2.8 if there was a strong clinical suspicion or unexplained progression of exertional dyspnoea.

Patients were divided randomly in a 2:1 ratio into derivation and validation cohorts by generating a random number between 0 and 1 for each patient, and allocating those with a number less than two thirds to the derivation cohort and the others to the validation cohort.

We then applied the formula to a separate population of patients with CTDs other than SSc who were referred to the Royal Free Pulmonary Hypertension service (London, UK) and underwent their first RHC between September 1996 and May 2010. There were 147 patients with a variety of CTDs in our database (59 SLE, 22 RA, 42 UCTD, 9 MCTD, 12 DM, 15 PM, 12 Sjogrens). Contemporary PFT data, within six months of the RHC, was available in 52 of these patients (SLE 17, UCTD 15, RA 7, DM 4, PM 3, MCTD 3, Sjogren's syndrome 2, HSP 1) and they were included in the validation analysis.

Clinical Data

Pulse oximetry measurements were taken at the time of the RHC. Data on smoking status weight and height were collected at the time of PFTs. PFTs were performed at the Royal Free

Hospital or the Royal Brompton Hospital. We defined PH as a resting mPAP of $\geq$25 mmHg.[14] Echocardiography was performed in the referring hospital or at the Royal Free Hospital. Pulmonary artery pressures were estimated from tricuspid jet maximal velocity using the simplified Bernoulli equation.

Data Analysis

Analyses were performed using STATA® software (STATA version 10.0 for Windows, Texas, USA). Data were expressed as means (SD) or medians (range), depending on distribution. Group comparisons were made using Student's *t* test or chi-squared as appropriate. A *P* value of less than 0.05 was considered significant.

Univariable linear regression was performed to identify variables of interest for the multivariable linear regression. Variables with statistical significance ($p<0.05$) were included in the multivariable linear regression. We found that DL_{CO} % predicted and SpO_2 explained 13-14% of the variability in mPAP ($p<0.0005$, R^2 was 13.1 and 13.7 respectively), K_{CO} % predicted provided similar information to DL_{CO} % predicted and other variables were less informative [Table 1]. We therefore proceeded to multivariable linear regression using DL_{CO} % predicted and SpO_2.

Table 1. Univariable regression against mean pulmonary artery pressures was performed in the 386 patients in the study to identify variables of interest.

Variable	P value	R^2
Gender	0.499	0.3%
Age	0.377	0.6%
DL_{CO} % predicted	<0.0005	13.1%
SpO_2	<0.0005	13.7%
FVC % predicted	0.023	1.4%
Scleroderma-70	0.002	2.9%
Centromere	0.006	2.3%
Smoker (0=never, 0.5=previous, 1=present)	0.138	0.7%
Weight	0.001	3.5%
Body Mass Index	0.069	1.0%

Using multiple variable linear regression in the derivation cohort, we explored the relationship between SpO_2, PFTs, clinical subtype, autoimmune serology and the mean pulmonary artery pressure (mPAP) on RHC and derived a formula for predicted mPAP.

We used split sample derivation and validation. We performed subgroup analysis by clinical subtypes (limited or diffuse), serological subtype (anti-centromere or anti-topoisomerase I (scleroderma-70) antibody), smoking status and lung function. We compared the performance of our formula to other existing formulae and to echocardiography. Finally, we tested the

formula in a population of patients with CTDs other than SSc who underwent RHC at the same institution over the same timeframe.

Results

Study Population

Within the study sample of 386 patients, 243 patients (63.0%) had pulmonary hypertension. The mean number of days between PFTs and RHC was 54.3 (SD 50.8). Comparing patients with PH (n=243, mean mPAP 37.7 mm Hg) to those without (n=143, mean mPAP 19.2 mm Hg), age and gender were similar. Oxygen saturation was lower in patients with PH (mean 94.3%) than in those without PH (mean 96.3%, $p<0.005$). Diffusion of carbon monoxide (DL_{CO}) % predicted was also lower in those with PH (mean 38.6%) than in those without (mean 50.0%, $p<0.005$). The subtype of scleroderma (limited or diffuse) was not associated with presence of PH ($p=0.75$). Patients with PH were more frequently anti-centromere antibody positive (n=206, 38.3%) than those without (n=131, 28.2%) although statistical significance was not reached ($p=0.057$ for comparison). Patients with PH were less likely to carry the anti-scleroderma-70 antibody (16.2%) than those without (28.5%, $p=0.007$).

Patients with pulmonary hypertension (n=243) were classified as respiratory disease associated (Group 3 in the Dana Point classification of pulmonary hypertension) in 113 patients (FVC predicted <80%), left heart disease associated (defined by pulmonary capillary wedge pressure above 15 mmHg at right heart catheterization) in 33 patients (Group 2) and pulmonary arterial hypertension in 114 patients (Group 1).

The derivation (n=257) and validation (n=129) cohorts were well matched with respect to age, gender, prevalence and severity of PH, clinical subtypes, PFT data, autoimmune serology and smoking status.

Identifying Variables of Interest

Univariate linear regression was performed to identify variables of interest for the multivariable linear regression. We found that DL_{CO} % predicted and SpO_2 explained 13-14% of the variability in mPAP ($p<0.0005$, R^2 was 13.1 and 13.7 respectively), K_{CO} % predicted provided similar information to DL_{CO} % predicted and other variables were less informative. We therefore proceeded to multivariable linear regression using DL_{CO} % predicted and SpO_2.

Derivation of a Formula Based On DL_{CO} % predicted and SpO_2

DL_{CO} % predicted and SpO_2 were both significantly associated with mPAP ($p<0.0005$). Regression using DL_{CO} % predicted and oxygen saturation gave R^2 of 23.1%. This gave a formula of predicted mPAP = 130.88 – 0.95 x SpO_2 – 0.24 x DL_{CO}% predicted. This can be simplified to:

Predicted mPAP = 136 – SpO_2 – 0.25 x DL_{CO} % predicted

No colinearity was found between SpO2 and DL_{CO} % predicted. We tested whether the time interval between RHC and PFT influenced the result by analyzing separately those patients in the derivation cohort who had PFTs within 60 days (n=154) and those whose PFTs were done more than 60 days before or after their RHC (n=103). The area under the curve was 0.75 in both cases (p=0.97), suggesting that the relationship between PFTs and presence of pulmonary hypertension is similar in the two groups.

Influence of Low Forced Vital Capacity on Multivariable Model

FVC % predicted did not associate with pulmonary artery pressures in multivariable linear regression (p=0.37). However, on separate analyses in patients with low or preserved FVC, a clear difference was seen between those with FVC<60% predicted (n=54, R^2=13.0%) and those with FVC≥60% predicted (n=203, R^2=35.0%).

Autoantibody Status

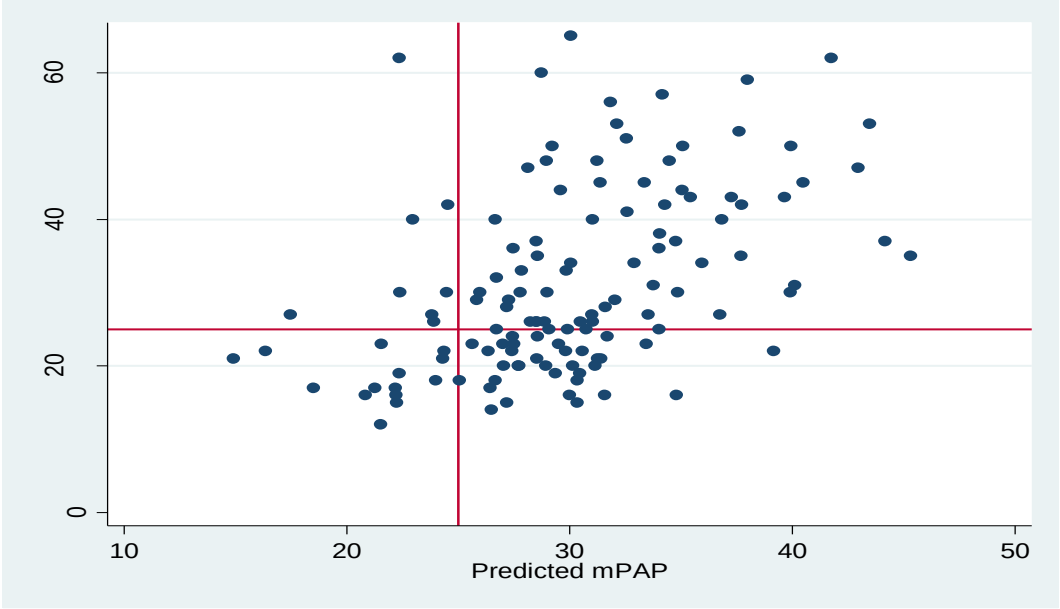
Compared to the simple model described above (DL_{CO} % predicted and Oxygen Category) addition of centromere antibody status (1 if positive, 0 if negative) was associated with mPAP

(p=0.006) and improved model fit (R^2 increases from 23.1 to 26.4). Scleroderma-70 antibody was more tightly associated (p<0.0005, R^2 increases from 23.1 to 27.1) and when both scleroderma-70 and centromere were added, scleroderma-70 remained strongly significant (p<0.0005) but centromere became non-significant (p=0.43).

Testing of the Formula in the Validation Cohort

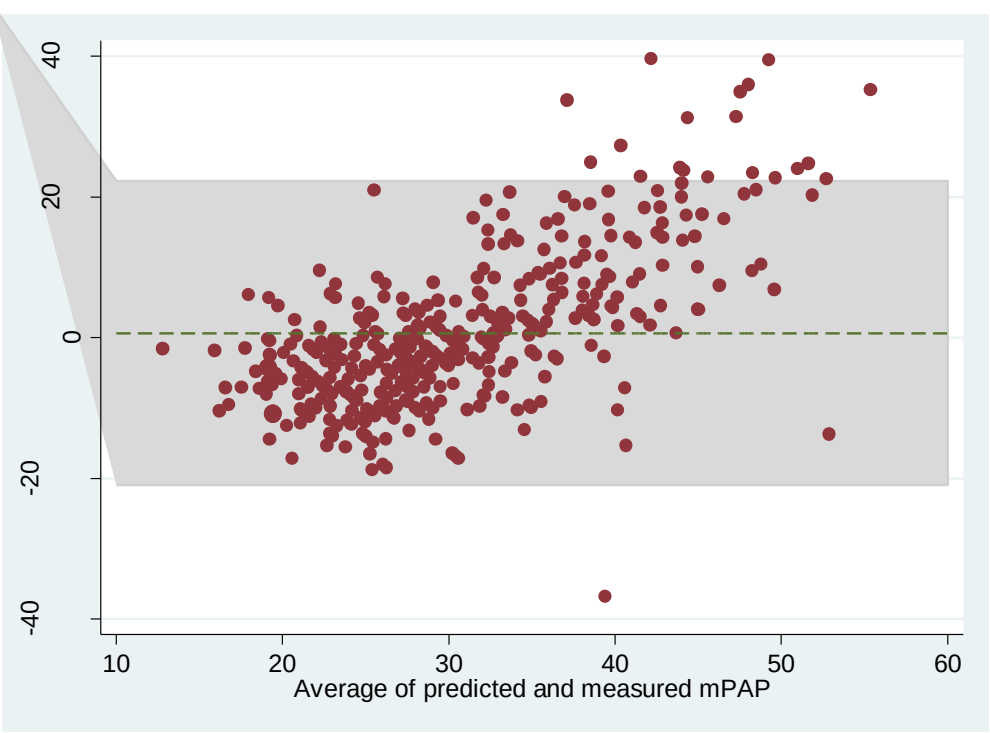
Applying this simplified formula in the validation cohort (n=129) gave an area under the curve of 0.75 (95% CI 0.67,0.84), and an R^2 value of 22.3%. A scatterplot is shown in Figure 1.

Figure 1. Scatterplot of predicted and measured mean pulmonary artery pressure in the validation cohort



Using a predicted threshold of 25 mmHg to diagnose pulmonary hypertension, the sensitivity was 90.1% (95% CI 82,96), specificity 29.2% (95% CI 17,44), positive likelihood ratio 1.3 (95% CI 1.05,1.55) and negative likelihood ratio 0.3 (95% CI 0.2,0.7). A Bland-Altman plot showed a mean difference between predicted and measured mPAP of 1.1 (95% limits of agreement -20.4,22.6). It can be seen that there is better agreement in lower pulmonary pulmonary artery pressures and a trend to underestimate very high pressures [Figure 2].

Figure 2. bland-altman plot showing level of agreement between formula predicted and actual right heart catheterisation



Using a predicted threshold of 30mmHg to diagnose pulmonary hypertension, the sensitivity was 59.3% (95% CI 47.8,70.1) and the specificity was 70.8% (95% CI 55.9,83.0). Using a predicted threshold of 35 mmHg to diagnose pulmonary hypertension, the sensitivity fell to 25.9% (95% CI 16.8,36.9) but the specificity rose to 97.9% (95% CI 88.9,99.9).

We can therefore estimate the prevalence of pulmonary hypertension in a typical scleroderma cohort with a prevalence of 12%.13 Patients with predicted mPAP below 25 mmHg have a low prevalence of pulmonary hypertension of 4.41% (95% CI 2.1,9.3). Those with intermediate predicted mPAP between 25 and 35 mmHg have an average risk of PH of 11.3% (95% CI 9.0,14.1). Those with a formula predicted mPAP above 35 mmHg have a high prevalence of PH of 62.9% (95% CI 19.1,92.4).

Thus, a predicted mPAP below 25 mmHg indicates a group with a low prevalence of PH. A predicted mPAP of 25-35 mmHg indicates a group with average incidence, and those patients

with formula predicted mPAP above 35 mmHg have a high prevalence of pulmonary hypertension.

Subgroup Comparisons

We explored the relationship between predicted and measured mPAP in subgroups within our combined study cohort. We examined the effect of disease subtype, autoantibody, restrictive lung disease, raised pulmonary capillary wedge pressures and smoking on the relationship between predicted and measured mPAP [Table 2].

Table 2. Results of linear regression to predict pulmonary artery pressures based on oxygen saturation and DL_{CO} in subgroups of patients with systemic sclerosis

	Number of patients	Area under the curve (95% CI)	Sensitivity	Specificity	R^2
All patients	386	0.75 (0.70,0.80)	90.9% (86.6,94.2)	35.0% (27.2,43.4)	22.8%
LcSSc	284	0.75 (0.70.0.81)	91.1% (86.0,94.8)	34.6% (25.6,44.6)	26.6%
DcSSc	91	0.74 (0.64,0.85)	89.3% (78.1,96.0)	37.1% (21.5,55.1)	10.0%
Anti-Centromere positive	116	0.87 (0.80,0.94)	89.9% (81.0,95.5)	62.2% (44.8,77.5)	41.8%
Scleroderma-70 positive	69	0.75 (0.64,0.87)	96.9% (83.8,99.9)	13.5% (4.54,28.8)	23.0%
FVC<80%	167	0.69 (0.61,0.77)	95.6% (90.0,98.5)	13.0% (5.4,24.9)	14.0%
FVC>80%	219	0.79 (0.73,0.85)	86.9% (79.9,92.2)	48.3% (37.6,59.2)	29.6%
Raised Pulmonary Capillary Wedge Pressure	34	0.60 (0.37,0.82)	76.9% (56.4,91.0)	50.0% (15.7,84.3)	17.8%
Smokers (past and present)	134	0.73 (0.63,0.82)	94.3% (87.2,98.1)	34.8% (21.4,50.2)	10.1%
Non-smokers	181	0.75 (0.68,0.82)	89.9% (81.7,95.3)	35.9% (26.1,46.5)	19.2%

It is notable that the formula performs well in patients with anticentromere antibodies, with an area under the curve of 0.87 (0.80,0.97). This may be because patients with anticentromere antibodies have less restrictive lung disease than other patients (mean FVC % predicted 100.2% in patients with anticentromere antibodies and 77.8% in patients without, $p<0.0005$ for the difference). Hypoxia in patients with anticentromere antibodies is therefore likely to directly reflect pulmonary vasculopathy. The prevalence of pulmonary hypertension was not significantly higher in patients with anticentromere antibodies than in those without (68.1% and 60.7% respectively, $p=0.17$ for the comparison).

Of the total 386 patients in our study, 34 had raised pulmonary capillary wedge pressure (>15mmHg). The area under the curve in these patients (0.60, 95% CI 0.37-0.82) was not different to the area under the curve for patients with normal wedge pressure (0.77, 95% CI 0.72-0.82, $p=0.15$ for the comparison). The sensitivity and specificity of the formula for predicting pulmonary hypertension in the validation cohort are not significantly affected by the removal of the patients with high wedge pressures (Sensitivity 93.0%, specificity 37.1% with these patients excluded, compared to sensitivity 91.4% and specificity 37.9% overall).

243 had pulmonary hypertension at right heart catheter (mPAP≥25mmHg). We analysed the performance of the formula in identifying pulmonary arterial hypertension (defined as mPAP≥25mmHg, pulmonary capillary wedge pressure ≤15mmHg, and FVC >80% predicted to exclude major interstitial lung disease). 115 patients of the 386 patients met this definition. In these patients, correlation between predicted and actual mean pulmonary artery pressures was 0.45 compared to 0.35 in the 243 patients with pulmonary hypertension.

In order to clarify the effect of interstitial lung disease on the formula, we analysed separately the performance of the formula in a subgroup of patients in the validation cohort with no significant restrictive lung disease (FVC > 80% predicted) and no interstitial lung disease on CT chest. The overall performance of the formula was not significantly improved in this group without significant lung disease (AUC 0.79, 95% CI 0.69-0.88) compared to patients in the rest

of the validation cohort (AUC 0.74, 95% CI 0.67-0.82, p=0.49 for the comparison). The incidence of pulmonary hypertension was not different in these two groups (66.0% in patients without lung disease, 61.2% in those with lung disease, p=0.45 for the comparison).

Comparison to Echocardiography

Echocardiography within three months of the RHC was available in 96 patients in our study (63 in derivation and 33 in the validation cohorts). In these patients, the AUC for echo derived TV gradient (AUC 0.73, 95% CI 0.63,0.83) was similar to that for the new formula in the same patients (AUC 0.75, 95% CI 0.64,0.86, p=0.78 for the comparison). There is similarly no difference between the AUC of echocardiography and the formula in the 63 patients in the derivation cohort alone (p=0.93 for the comparison). Using an echocardiographic cut-off of tricuspid regurgitant velocity > 2.8 m/s, sensitivity was 73.3% (95% CI 60.3, 83.9) and specificity 44.4% (95% CI 27.9,61.9). With the higher recommended cut off of TR jet velocity > 3.4 m/s, sensitivity was 33.3% (95% CI 21.7,46.7) and specificity was 97.2% (95% CI 85.9,99.9).

Logistic regression shows that after adjustment for echocardiography patients with formula predicted mPAP of 25mmHg or more have an odds ratio of 10.3 (95% CI 1.5-54.1, p=0.006) for the presence of pulmonary hypertension in the validation cohort (n=63), and an odds ratio of 9.2 (95% CI 2.6-32.5, p=0.001) for pulmonary hypertension in both cohorts combined (n=96).

In fact, logistic regression in the 25 patients who had echo RVSP in the range considered equivocal in current guidelines (RVSP between 37 and 50) showed that in these patients a formula predicted mPAP of 25mmHg or more is associated with an odds ratio of 12.8 (95% CI 1.0-157.1, p=0.047) for the presence of pulmonary hypertension.

In order to further clarify the additional diagnostic utility over echocardiography, two models were compared. Linear regression using echo-RVSP alone gave R^2=40.3 (p<0.0005). Repeating the model with echo-RVSP and the formula result (136-SpO2-0.25 x DLco % pred) has a better fit (R^2=62.2, p<0.0005 for both echo-RVSP and formula result). Likelihood ratio test indicates

improvement of the model (p=0.0001). This demonstrates that the formula adds significantly more information than is available with echocardiography alone.

Combination with Echocardiography

Separate analysis was performed in 96 patients with echocardiography and pulmonary function tests contemporary to the right heart catheter. Both echocardiographic and formula results were converted to categorical variables: echocardiography using the guidelines (0 if RVSP<37 mmHg, 1 if RVSP≥37 and ≤50 mmHg, 2 if RVSP>50mmHg) and the lung function formula (0 if predicted mPAP<25, 1 if predicted mPAP 25-35, 2 if pred mPAP>35). Multivariable Logistic regression shows similar odds ratios for each increase in Formula category (odds ratio 3.9, p=0.003, CI 1.6-9.6) and Echo category (odds ratio 3.2, p=0.009, CI 1.3,7.5), and there is no interaction between the two scores (p=0.45 for interaction term).

The PFT formula we have suggested can be combined with RVSP on echocardiography to give a simple score (formula category + echo category) between 0 and 4. This score has an area under the curve of 0.78 (0.70-0.87) for presence of pulmonary hypertension on right heart catheterisation. A score of 2 or more has a sensitivity of 80.6% (95% CI 64.0,91.8) and a specificity of 63.3% (49.9,75.4) for the presence of pulmonary hypertension. A score of 3 or more has a sensitivity of 28.3% (95% CI 17.5,41.4) and a specificity of 97.2% (95% CI 85.5,99.9) for the presence of pulmonary hypertension.

In a typical scleroderma population with a prevalence of pulmonary hypertension of 12%, a score below 2 will be reassuring with an associated prevalence of PH 5.8% (4.1,8.4), a score of 2 will be concerning, with an associated prevalence of PH of 28% (15,46.1) and a score of 3 or 4 is predictive of PH with a prevalence of 58.2% (16.2,90.9). This simple score allows combination of echocardiography with pulmonary function testing and facilitates decision making in patients with equivocal results in either test.

Validation of the Pulmonary Function Test Formula in non-Scleroderma Connective Tissue Disease

We then tested the formula in 53 patients with non-SSc CTD who underwent their first RHC at the same time in our institution.

Application of the formula in this population gave an AUC of 0.64 (95% CI 0.45,0.84). Using a threshold of 25mmHg the sensitivity was 92.9%, specificity 18.2%, positive likelihood ratio 1.1, negative likelihood ratio 0.4. The high sensitivity is encouraging but the positive predictive value will depend on the prevalence of pulmonary hypertension in the population under consideration.

Performance of Other Proposed Formulae

In our entire study population (n=386) we compared performance of our formula and recommended thresholds with that of others, and provide p values for significance of difference in areas under the curve between our own formula and the others [Table 3].

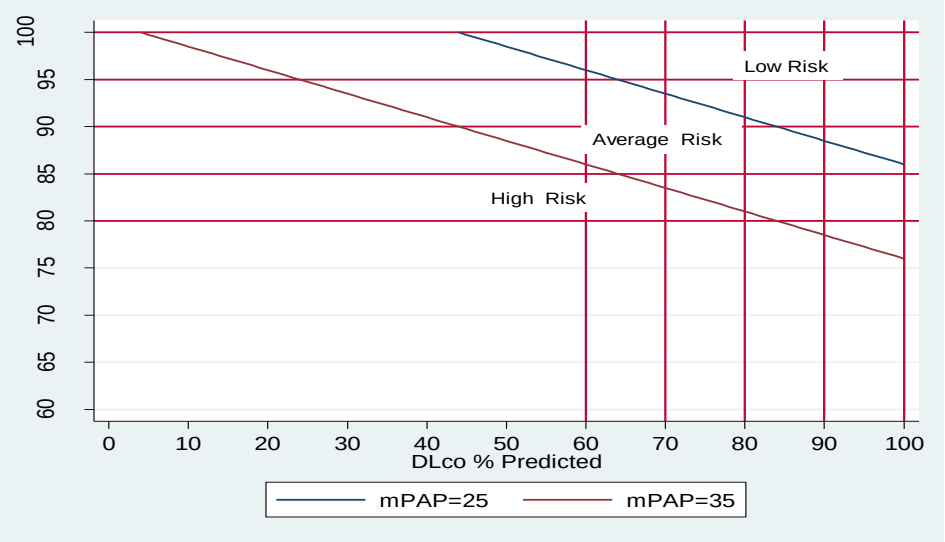
Table 3. Comparison of performance of our formula to other formulae for predicting mPAP based on pulmonary function data in all 386 patients

	Area under curve (95% CI)	Threshold	Sensitivity	Specificity	P value
Our formula	0.75 (0.70,0.80)	>25	91.0%	35.0%	
		>35	29.2%	95.1%	
ILD formula[5]	0.71 (0.66,0.76)	>25	29.6%	94.4%	0.075
FVC/DL_{CO}	0.66 (0.60,0.71)	>1.4	89.3%	22.4%	<0.001
		>2	55.6%	67.1%	
DL_{CO}/VA	0.70 (0.65,0.76)	<70%	79.0%	46.9%	0.082
		<60%	58.4%	71.3%	

Discussion

In our large cohort of patients with systemic sclerosis we have derived and validated a formula to improve detection of pulmonary hypertension using pulse oximetry and diffusion of carbon monoxide: Predicted mPAP = 136 – SpO_2 – 0.25 x DL_{CO}% predicted. A simple nomogram may be used to quickly establish if a patient is in the low risk (predicted mPAP < 25 mmHg), average risk (predicted mPAP 25-35mmHg) or high risk (predicted mPAP > 35 mmHg) categories (Figure 3).

Figure 3. Nomogram showing which patients with systemic sclerosis have predicted mean pulmonary artery pressures below 25 mm Hg (low risk), 25-35 mm Hg (average risk) or above 35 mm Hg (high risk) based on DLCO and oxygen saturation.



Low risk patients are unlikely to have pulmonary hypertension (prevalence 4%, 95% CI 2-9). High risk patients are likely to have pulmonary hypertension (prevalence 63%, 95% CI 19-93). In the average risk patients the results do not markedly change the pretest probability of pulmonary hypertension (prevalence 11%, 95% CI 9-14, compared to background assumed prevalence in the group of 12%). We suggest that patients at high risk should be considered for right heart catheterization while those at low risk can be reassured, and a longer follow-up period may be considered. In the intermediate group, management is unchanged.

Our analysis was geared particularly to establishing the diagnostic value of pulmonary function tests in detecting pulmonary hypertension in systemic sclerosis. In this 'real life' cohort, different causes of pulmonary hypertension were diagnosed, including pulmonary hypertension associated with respiratory disease (group 3) and cardiac disease (group 2) as well as pulmonary arterial hypertension (group 1). Diagnosis of pulmonary hypertension is important in all patients. In patients with interstitial lung disease, those with pulmonary hypertension have a worse prognosis than those without, and diagnosis aids in counseling and planning. Pulmonary hypertension due to left heart disease can and should be treated and is associated with an

adverse prognosis where pulmonary hypertension is present. Thus, detection of pulmonary hypertension is important in all patients in systemic sclerosis.

The formula explains only 23% of the variability in pulmonary artery pressures, which is reflected in the wide confidence intervals for agreement between predicted and measured pulmonary artery pressures. However, the receiver operating characteristics show that it performs well at predicting presence or absence of pulmonary hypertension.

Echocardiography is widely used as the primary non-invasive test of pulmonary artery pressures. Analysis of echocardiographic data in our patients has shown that the two tests provide complementary information and that information derived from pulmonary function tests is as predictive as echocardiography. Our analysis combining echocardiography with pulmonary function tests shows a high prevalence of pulmonary hypertension in patients with a high result for either or an equivocal result for both. Patients with an equivocal result in one test and a reassuring result in the other are less likely to have pulmonary hypertension.

We have shown that in patients with anti-centromere antibodies the formula performs particularly well. The difference in antibody subgroups may be partially explained by a higher prevalence of interstitial lung disease in patients with anti-scleroderma-70 antibodies. However, correcting for FVC does not improve the model. The differences may be due to lung changes which are not reflected in the forced vital capacity, or FVC may be reduced in patients with PAH who are breathless.

Our analysis shows that disproportionate reduction in oxygen saturation for a given DL_{CO} % predicted is seen in pulmonary hypertension. This mirrors the findings of Zissman et al in idiopathic interstitial lung disease.[15] It seems that oxygen saturation and DL_{CO} are influenced by somewhat different physiological components each of which impact on pulmonary artery pressures. DL_{CO} correlates with extent of fibrosis on HRCT in systemic sclerosis.[16] Hypoxaemia may relate in addition to severe vascular intimal remodeling and obliteration causing ventilation-perfusion mismatch and to shunting through a patent foramen ovale. Pulmonary

vasculopathy may be associated with impaired hypoxia induced vasoconstriction which profoundly amplifies ventilation-perfusion mismatch causing disproportionate hypoxia.[17]

Our results can be compared with other reported studies. A high ratio of FVC to DL_{CO}% predicted was associated with pulmonary arterial hypertension in 49 patients with systemic sclerosis,[18] and a low DL_{CO}/VA was associated with subsequent development of pulmonary hypertension in 110 patients in France.[19] In patients with idiopathic pulmonary fibrosis, a formula based on pulmonary function tests and oxygen saturation can help detection of pulmonary hypertension.15

Echocardiography is a recommended tool for the non-invasive diagnosis of pulmonary hypertension.[20,]14 However, echocardiography cannot assess lung disease and is not always technically possible. Even when performed within one hour of the right heart catheter there is only moderate agreement between echocardiography and right heart catheter pulmonary artery pressures.[21] Patients with scleroderma require regular pulmonary function tests including DL_{CO} to screen for interstitial lung disease.[22,23,24] Using our formula, these tests can be used to detect patients more likely to have pulmonary hypertension, making this a more cost effective test.

Strengths of our study include the large patient cohort, the inclusion of clinical diagnoses, serology and oxygen saturation and the completeness of right heart catheter data. In addition, we have been able to derive and validate our formula in separate but comparable patient groups, and to test it in a different patient population with connective tissue diseases other than scleroderma.

Our study had limitations. The prevalence of pulmonary hypertension in the cohort was 63%, which indicates that the current decision rules for selection of patients for right heart catheter are fairly effective. Use of this formula would allow for further refinement. Patients without PFT data were excluded from the study. However, this is unlikely to have affected the results because the patients who were excluded had similar incidence and severity of PH. We have not included high resolution CT data and have used FVC % predicted to distinguish patients with

pulmonary arterial hypertension from pulmonary hypertension due to lung disease. We have shown subgroup analysis for those with preserved FVC and for patients with normal wedge pressures. It is not known whether lung disease which does not affect lung function may cause secondary hypertension. We did not have echocardiographic data for most patients and there may have been selection bias in the patients who had echocardiography repeated at our hospital, so the comparison to echocardiography was limited and should be repeated in a prospective cohort.

Further work should explore combining pulmonary function test data with other non-invasive information such as symptoms, six minute walking distance and brain natriuretic peptide levels. Prospective validation of this formula may be possible in patients recruited to the DETECT study, a prospective, observational, cohort study in scleroderma patients to evaluate screening tests. [25] Other important initiatives including the Pulmonary Hypertension Registry of Scleroderma (PHAROS) and the ItinerAIR Scleroderma Study Group are furthering our understanding of the clinical utility of non-invasive testing for earlier detection of pulmonary hypertension.

In conclusion, we have shown that pulmonary function tests and pulse oximetry are useful in screening for pulmonary hypertension, providing information which is complementary to echocardiography. Using this simple formula may assist in interpretation of pulmonary function tests performed as routine screening in patients with systemic sclerosis and in better selection of patients for right heart catheterization.

Chapter 2. Combining non-invasive tests to diagnose pulmonary hypertension

***Schreiber BE**, Valerio CJ, Handler C, Keir G, Wells AU, Denton CP, Coghlan JG. A new formula to Predict Pulmonary Artery Pressures in Patients with Connective Tissue Disease based on Echocardiography, NTproBNP and O_2 Saturation.*

Oral presentation. ACR, Atlanta, November 2010

Abstract

Introduction

Pulmonary Hypertension (PH) is an important complication of connective tissue disease (CTD). Diagnosis is confirmed by right heart catheter (RHC) but no single non-invasive test accurately predicts PH. To improve selection of patients for RHC, we analysed the relationship between non-invasive tests and mean pulmonary artery pressure (mPAP) at RHC and derived a new formula to predict PAP.

Methods

Retrospective analysis of patients with CTD undergoing a first RHC. In our database we have 968 patients (811 SSc, 53 SLE, 15 RA, 42 UCTD, 8 MCTD, 12 DM, 7 PM, 6 Sjogrens, 3 antiphospholipid syndrome, 3 vasculitis). We included for analysis NTproBNP and echocardiography if performed within 3 months of RHC and pulmonary function tests if done within 6 months. Pulse oximetry was measured at the time of the RHC.

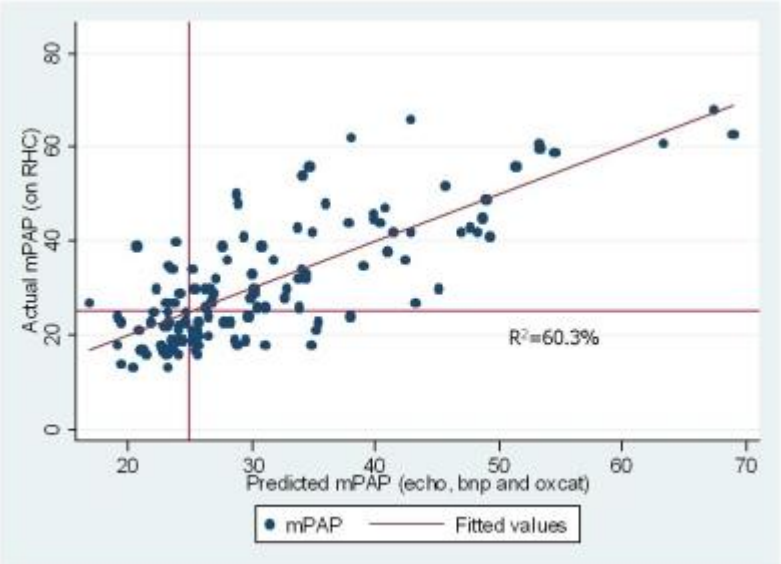
Results

Regression analysis of these variables individually against mPAP at RHC gave the following results: DL_{CO} (n=469) gave R^2=8.7, AUC=0.68; NTproBNP (capped at 300 pmol/litre to reduce the skewing effect of large values) with n=380, gave R^2=31.5, AUC=0.74 and echo derived tricuspid valve gradient (n=165) gave R^2=48.9, AUC=0.81. Capping NTproBNP gave similar results to a log transformation.

Multivariable linear regression showed significant correlation with mPAP for Echo derived TV gradient (p<0.0005), capped NTproBNP and Oxygen (p=0.004). Addition of predicted DL_{CO}, K_{CO}, FVC, weight or height did not improve the fit. To reduce heteroskedasticity, oxygen was used categorically (1 if SpO_2 >94%, 2 if 90-94%, 3 if <90%). Based on all 123 patients for whom we had NTproBNP, echo and SpO_2 data, the derived formula is:

Predicted mPAP = 8.37 +3.83 x Oxygen category + 0.328 x Echo derived Tricuspid Valve gradient + 0.032 x NTproBNP (capped)

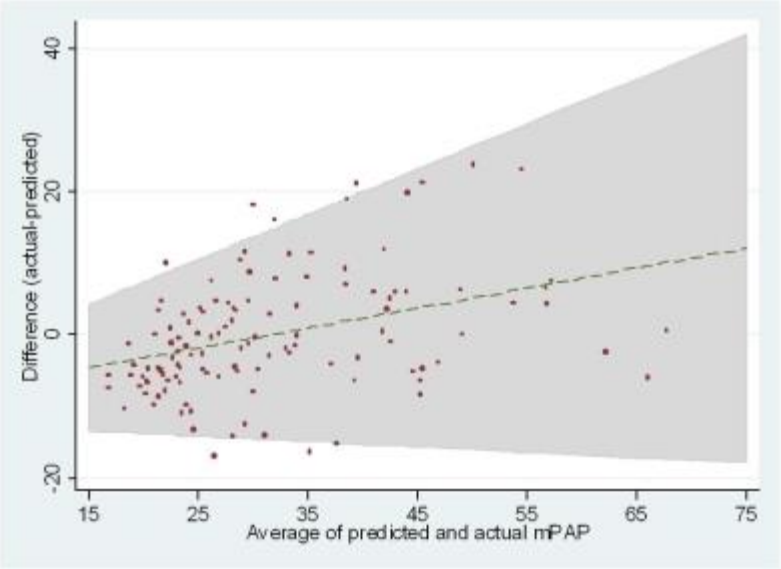
This formula had R^2 of 60.3%.



The area under the curve was 0.84 (95% CI 0.77-0.91). Using a threshold predicted mPAP of 25 it has a sensitivity of 87.3%, specificity of 55.8%, positive LR of 2.0 and negative LR of 0.2.

Using a threshold predicted mPAP of 30, it has a sensitivity of 66.2%, specificity of 90.4%, positive LR of 6.9, negative LR of 0.4.

Bland-Altman analysis showed a mean agreement of -0.6 (95% CI -16.4, 16.3) for difference between predicted and actual mPAP, although as seen in the figure, the 95% CI are tighter at lower predicted values.



This compares favourably with echocardiography done within 1 hour of the RHC (Fisher MR et al, Am J Respir Crit Care Med. 2009).

Conclusions

This formula may help identify CTD patients requiring RHC. Patients with a formula predicted mPAP under 25 are unlikely to have PH, and those patients with predicted mPAP above 30 are very likely to have PH.

Introduction

Pulmonary Hypertension (PH) is an important complication of connective tissue diseases, occurring in about 12% of patients with Systemic Sclerosis (SSc) and less commonly in other rheumatic diseases.13 Right heart catheterization (RHC) is the gold standard diagnostic test but it is invasive. European guidelines suggest use of echocardiographically estimated right ventricular systolic pressure (RVSP) based on tricuspid regurgitant jet maximal velocity (TR V_m) with three arbitrary categories: unlikely (RVSP<36), possible (RVSP 36-50) and likely (RVSP>50).14 It is not clear how echocardiography should be interpreted with respect to patients' symptoms or to lung function tests.

We have recently shown that a formula based on pulmonary function tests (predicted mPAP = 136 - SpO2 - 0.25 x DLco% predicted) is associated with the presence of pulmonary hypertension in patients with systemic sclerosis.[26] Other non-invasive measures such as functional class, six minute walking distance, NT-pro-BNP and pulmonary function tests have been shown to correlate with presence of PH on RHC. However, it is not known whether using a combination of non-invasive measures can predict the presence of PH better than using RVSP alone. Using a large database of patients with connective tissue disease who have undergone RHC, we sought to explore the optimal combination of non-invasive tests.

Patients and Methods

We analysed data from 152 patients with SSc who underwent a first RHC at a PH referral centre between 2005 and May 2010 and who had contemporary echocardiography (Royal Free Hospital, London, UK).

The mean age was 59 years and 17% of the patients were male. 59% were found to have PH at RHC. Skin involvement was limited in 70% and diffuse in 30%.

We analysed each of the non-invasive diagnostic tests in turn, to examine how informative each test is in predicting presence of PH using receiver operating characteristics. Correlation

coefficients of each parameter against mean pulmonary artery pressure (mPAP) were also calculated.

We used correlation coefficients to examine the correlation between test result and mPAP on RHC. Receiver operating characteristics were assessed and area under the curve was calculated to provide an estimate of the diagnostic utility of the test in establishing presence or absence of PH. Logistic regression was used to identify combinations of variables which predict presence of PH. We then applied the findings to calculate positive predictive values in a typical SSc population with a prevalence of PH of 12%.

Results

We first analyzed the relationship between individual variables and the presence of PH, using receiver operating characteristics and univariable logistic regression (Table 1). In our pulmonary hypertension enriched population of 100 patients with echocardiography suggesting PH is "unlikely" according to current guidelines (RVSP<36), 42 had pulmonary hypertension, highlighting the high rate of false negatives with this test.

Univariate analysis was performed for baseline demographic, pulmonary function tests, six minute walking distance, NTproBNP, functional class, and echo derived RVSP against pulmonary hypertension at RHC.

Table 1. Univariable Analysis of variables associated with the presence of pulmonary hypertension

	Odds ratio	95% CI	P value
Age	0.99	0.96,1.02	0.358
Gender	1.02	0.44,2.40	0.959
6MWD	0.99	0.99,0.10	0.011
O2 SATn	0.87	0.77,0.98	0.021

DLco %	0.95	0.92,0.98	<0.0005
PFT formula	1.16	1.06,1.26	0.001
WHO FC	4.62	2.21,9.64	<0.0005
NT-proBNP	1.004	1.001,1.008	0.009
ECHO rvsp	1.10	1.06,1.14	<0.0005

We repeated analysis of the non-invasive diagnostic tests described individually above using logistic regression. On multivariate analysis, the echo category, functional class category and pulmonary function test category were independently predictive of presence of pulmonary hypertension (Table 2).

Table 2. Multiple Variable Logistic Regression using Categorical values for functional class, echocardiographic RVSP and NT-pro-BNP

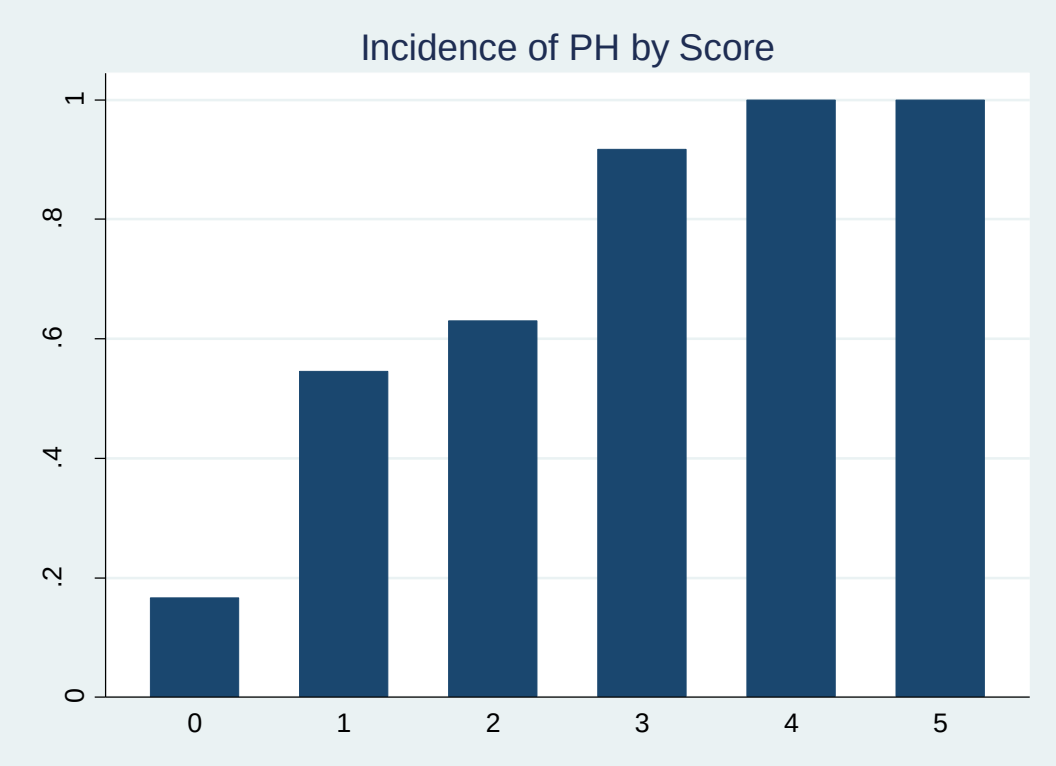
	Values	**Odds ratio**	**CI**	**P value**
Functional Class category	0: FC I/II 1: FC III/IV	4.19	1.1, 16.2	0.037
Echo category	0 : RVSP <36 1 : RVSP 36-50 2 : RVSP >50	3.94	1.3, 11.7	0.014
PFT formula (136-SpO2-0.25*DLco %)	0: <25 1: 25-35 2: >35	3.39	1.0, 11.4	0.048

We therefore generated a score to calculate the combined risk based on these variables:

Table 3. Components of score

Score	0	1	2
PFT formula (136-SpO2-0.25xDLco% predicted)	<25	25-35	>35
Echo RVSP	<36	36-50	>50
Functional class	I,II	III,IV	

The higher the score the greater the proportion of patients with pulmonary hypertension (odds ratio 3.8, p<0.0005, 95% CI 2.0-7.1) [Figure 1].



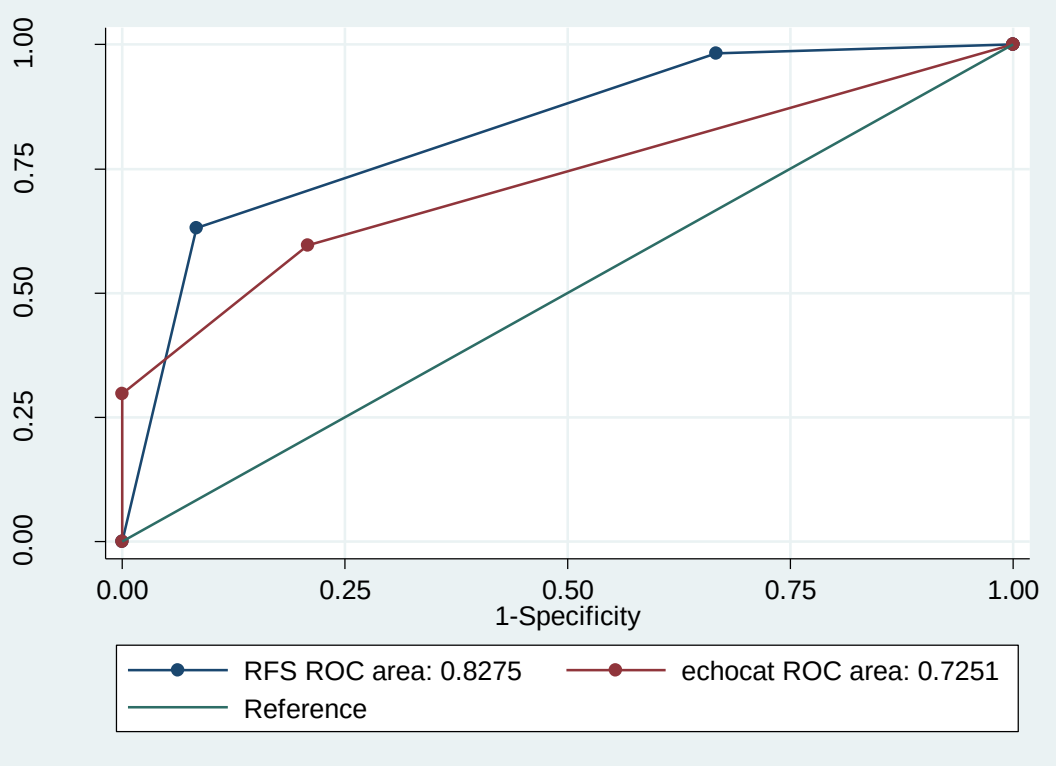
These fall into three groups: PH unlikely (score of 0), PH possible (score of 1-2) and PH likely (score of 3-5). These categories form the Royal Free Score (RFS).

RFS	**0**	**1-2**	**3-5**
No PH	8	14	2
PH confirmed	1	20	36

We are thus able, using a combination of functional class assessment, echocardiography and pulmonary function tests, to **exclude pulmonary hypertension in patients with score 0** (negative predictive value 88.9%, 95% CI 51.8-99.7%) and to **diagnose pulmonary hypertension in those with score of 3-5** (positive predictive value 94.7%, 95% CI 82.3-99.4%).

This score is more tightly associated with pulmonary hypertension than the current echocardiograpic guidelines (AUC 0.83 for RFS compared to 0.73 for TR Vmax, p=0.048 for comparison) (Figure 2).

[Figure 2]



The score was derived in a PH enriched cohort with a prevalence of PH of 61% and would be applicable to a similar population seen in pulmonary hypertension clinics and selected for right heart catheterisation. We can extrapolate to calculate positive and negative predictive values if this score is applied to screening investigations in a typical SSc population with a prevalence of PH 12%. If used as a screening test in a general systemic sclerosis cohort with a prevalence of pulmonary hypertension of 12%, prevalence of PH would be 0.7% (0.1-5.1%) in those with RFS 0, 16.9% (12.8-22.1%) in those with RFS 1 and 50.8% (21.3-79.8%) in those with RFS 2. Thus in a screening setting in a general SSc population, patients with a RFS 0 can be reassured, while those with a score of 2 should be considered for RHC. Patients with a score of 1 would remain under closer follow up, perhaps with six monthly review.

Summary

Our findings suggest that selection of patients for RHC can be improved by integration of echocardiography with other non-invasive measures, specifically pulmonary function tests and functional class assessment. This score combines anatomical and physiological information with

functional assessment and may enable better integration of currently disparate non-invasive testing in order to better select patients for RHC.

Screening programs allow for detection of patients with milder pulmonary hypertension.[27] However, screening programs based on echocardiography alone have found high false positive and false negative rates. The UNCOVER study showed that echocardiography suggested pulmonary hypertension was likely (RVSP>50mmHg) in 22.5% of patients with systemic sclerosis or mixed connective tissue disease in community rheumatology practices.[28] Previous studies in SSc have evaluated the reliability of prospective screening of patients with SSc based on tricuspid regurgitation velocity of 2.5-3.0 m/s in symptomatic patients (functional class II-IV) or 3.0 m/s irrespective of symptoms. They found that 45% of cases of echocardiographic diagnoses of PH were falsely positive.[29] The true incidence of false negative cases is not known.[30]

By comparison, our findings suggest that pulmonary hypertension can be excluded in patients with normal echocardiography, low risk pulmonary function tests (136-SpO2-0.25*DLco% predicted<25) and little or no breathlessness (FC I/II). The study has limitations due to its retrospective nature. In addition, we have analysed data on patients selected for right heart catheterization. It should therefore be seen as hypothesis generation for testing in a prospective data set. Validity can be explored in other large well characterized scleroderma cohorts and the ongoing DETECT study will offer an opportunity for prospective validation.

Chapter 3. Borderline pulmonary hypertension – What predicts progression in systemic sclerosis?

Schreiber BE, Valerio CJ, Handler C, Denton CP, Coghlan G. Predictors of Progression to Pulmonary Hypertension in Systemic Sclerosis. Abstract no 11-3526. EULAR, London, May 2011.

Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. Valerio CJ, Schreiber BE, Handler CE, Denton CP, Coghlan JG. Arthritis Rheum. 2013 Apr;65(4):1074-84.

Abstract

Background

In patients with systemic sclerosis (SSc) who undergo right heart catheterisation (RHC) and are not found to have pulmonary hypertension (PH), it is not clear which parameters predict future progression to pulmonary hypertension.

Objectives

We sought to clarify which haemodynamic parameters predict future progression to PH in patients with SSc.

Methods

Data on all RHCs in a PH referral centre were collected prospectively. Criteria for first RHC were based on standard screening algorithms incorporating clinical and laboratory assessment. We analysed all patients with SSc who underwent RHC, to find predictors of

progression to PH (n=340). Logistic regression was used to calculate predictors of future PH and Kaplan-Meier survival analysis to calculate difference in outcome between groups.

Results

For the 340 patients with SSc who underwent repeat RHC, mean age was 58.6 years, 80% were female and 77% had limited scleroderma.

Data from the first RHC showed: 45 normal mPAP (≤ 20mmHg, mean PVR 163 dynes.s.cm^{-5}), 49 borderline (mPAP 21-24, mean PVR 220), 65 mild PH (mPAP 25-29, mean PVR 280) and 181 with mod-severe PH (mPAP ≥ 30, mean PVR 663).

Of patients with normal mPAP, 30% progressed in 5 years, compared to 58% of those with borderline values. Mean time to progression was 74 months (95% CI 67.9-) in those with normal mPAP at baseline and 41 months (95% CI 26.1-67.9) in those with borderline mPAP at baseline (p=0.02 by log-rank for survival free of PH).

Univariate logistic regression showed poor correlation with baseline functional class, presence of fibrosis, age, gender, disease subtype (limited vs diffuse), body surface area, heart rate, right atrial pressure, and cardiac output, CO. There was significant correlation with mPAP (p=0.03) and pulmonary vascular resistance, PVR (p=0.02) and a trend with pulmonary capillary wedge pressure, PCWP (p=0.07).Mean mPAP in patients who progressed to PH was also higher than in patients who did not (21.1 vs 19.8, p=0.03).

Patients with initial mPAP above 20 had a trend towards progression to PH (odds ratio 2.0, 95% CI 0.9-4.7, p=0.11). The trend loses significance when adjusted for high PVR (p=0.48) while high PVR remains significant (odds ratio 3.1, p=0.02). High PVR is a particularly strong predictor amongst patients without lung fibrosis (OR 7.4, 95% CI 2.2-25.5, p=0.001).

Kaplan-Meier survival analysis to show proportion of patients surviving without progression to PH was performed. There is a clear divergence between those with PVR >200 and those <200 dynes.s.cm^{-5}, (p=0.003 by log-rank test).

Annual progression to PH is 18.7% in those with PVR>200 and 7.4% in those without giving an incidence rate ratio of 2.5 (95% CI 1.2-5.6) for those with PVR>200 compared to those with low PVR.

Conclusions

In patients with systemic sclerosis who do not have pulmonary hypertension on right heart catheterisation, patients with PVR above 200 dynes.s.cm^{-5} are at high risk of future progression to pulmonary hypertension. Repeat RHC should be considered in these patients.

Introduction

The definition of pulmonary hypertension continues to hinge on a single threshold of mean pulmonary artery pressure. However, the disease is clearly a continuum of increasing pulmonary vascular resistance causing a compensatory increasing pulmonary artery pressure. It has long been established that normal resting pulmonary artery pressures are under 20 mmHg, in fact they are more like 14.0 ± 3.3 mmHg.[31] 20 mmHg represents a level 2 standards of deviation above the mean. This clearly leaves an interval of 21-24 where there is an abnormal pulmonary artery pressure not diagnostic of pulmonary hypertension. Little is known about the prognostic meaning of such borderline results.

Methods

For these analyses we reviewed retrospectively all patients with connective tissue diseases who underwent a first right heart catheterization at our Institution. Inclusion criteria were: Connective tissue disease diagnosis, no clinical diagnosis of pulmonary fibrosis at the time of right heart catheterization, FVC >70% where available and pulmonary capillary wedge pressure ≤15mmHg. Mortality data was censored at 5 years follow up. Pulmonary function tests were included if performed within six months of right heart catheterization.

Patients with any underlying condition were included. The present analysis considered only those patients who had more than one right heart catheterisation. The right heart catheterisations were performed for clinical indications including unexplained breathlessness, unexplained low transfer of carbon monoxide, evidence of pulmonary hypertension on echocardiography (tricuspid regurgitant maximal velocity > 3.0 m/s).

636 patients with connective tissue disease underwent right heart catheterization. We grouped the patients by the mean pulmonary artery pressure at the initial right heart catheter study.

We classified patients into four groups based on the mPAP. Group 0 (normal) had mPAP≤20, Group 1 (borderline) had mPAP 21-24, Group 2 (mild PH) had mPAP 25-29 and group 3 (moderate-severe PH) had mPAP≥30.

Group 0 patients are younger than Group 1-3 patients (p=0.02) but there was no difference between groups 1, 2 and 3 (p=0.29 by ANOVA). There was no difference in gender between the groups (p=0.63 by ANOVA). Results are shown in figure 1.

Results

539 patients had repeat right heart catheterisations. The average age was 58.5 ± 13.3. 76.6% were female. 63.1% had systemic sclerosis (340 patients, 263 LcSSc, 77 DcSSc). Pulmonary fibrosis was present in 29% of patients. Pulmonary hypertension (mPAP ≥ 25 mmHg) was diagnosed in 80.9% of those who had subsequent right heart catheterisations. Of these patients 340 patients had systemic sclerosis. Of them, 36% had pulmonary fibrosis.

Figure 1. Baseline characteristics on right heart catheter of patients with connective tissue disease

	Definition	n=	Mean mPAP	Mean PVR	Cardiac Output	Mean Dlco % (n)	Age
Group 0	mPAP < 21	176	17.0	144.6	4.9	58.4 (62)	58.3
Group 1	mPAP 21-24	102	22.2	199.7	5.1	54.1 (41)	61.2
Group 2	mPAP 25-29	95	26.8	274.7	5.1	49.7 (42)	62.2
Group 3	mPAP ≥ 30	263	45.2	772.7	4.3	40.7 (115)	60.1

As expected, the bulk of the patients had scleroderma as their connective tissue disease. There is a trend towards more patients with anti-centromere antibodies in Group 1 than in Group 0 (p=0.08) but the proportion of patients with Scl-70 is similar in Group 1 and Group 0 (p=0.48).

Figure 2. Connective tissue disease subtype and presence of ACA and ATA profiles

	Scleroderma	Centromere	Scl-70	SLE
Group 0	85.2%	41.8%	13.0%	8.0%
Group 1	90.1%	58.1%	18.0%	0.0%
Group 2	84.2%	67.3%	8.8%	6.3%
Group 3	79.5%	67.2%	1.3%	8.0%

Haemodynamic profile

Baseline PVR is higher with each subsequent group ($p<0.00005$ for each comparison). Cardiac output in similar in groups 0 and 1 ($p=0.32$) and groups 1 and 2 ($p=0.94$). There is no difference in cardiac output across groups 0-2 ($p=0.52$ by ANOVA). However, there is a clear difference between group 2 and group 3 ($p<0.0005$). Wedge pressures was higher in group 1 than group 0 ($p<0.0005$), similar in groups 1 and 2 ($p=0.32$) and worse in group 3 than in group 2 ($p=0.01$).

Figure 3. Average pulmonary capillary wedge pressure in each group

	Mean wedge pressure	Standard Error	95% CI for Mean
Group 0	8.59	0.20	8.19-8.99
Group 1	10.27	0.26	9.76-10.79
Group 2	10.66	0.29	10.10-11.22
Group 3	9.80	0.18	9.45-10.15

We have only studied patients who had no clinical diagnosis of interstitial lung disease and with FVC > 70 % predicted where known.

Figure 4. Pulmonary function tests results in each group

	Definition	Patients with PFTs/Total (%)	Mean FVC %	Mean Dlco %	Age
Group 0	mPAP<21	62 / 176 (35)	99.9	58.4	58.3
Group 1	mPAP 21-24	41 / 102 (40)	103.9	54.1	61.2
Group 2	mPAP 25-29	42 / 95 (44)	98.6	49.7	62.2
Group 3	mPAP ≥30	115 / 263 (44)	95.1	40.7	60.1

FVC does not vary between groups 0,1 and 2 (mean 100.7 % predicted, p=0.31 by ANOVA) but is lower in group 3 than in groups 0,1 and 2 combined (p=0.008). There is a trend to lower DLco in group 1 than in group 0 (p=0.15), and for lower DLco in group 2 than in group 1 (p=0.17). Group 2, however, is clearly lower than Group 0 (p=0.002) and there is a further clear drop between groups 2 and 3 (p=0.0002).

Functional class was scored for most patients (n=567 of 636) at the time of right heart catheterization. Mean functional class in each group is shown in the figure. Functional class in groups 0 and 1 were similar (p=0.76). It was worse in group 2 than group 1 (p<0.0005) and worse in group 3 than group 2 (p<0.0005).

Figure 5. WHO Functional class by group

	Mean functional class	Standard Error	95% CI for Mean
Group 0	2.32	0.06	2.20-2.44
Group 1	2.29	0.07	2.16-2.43
Group 2	2.73	0.06	2.61-2.84
Group 3	3.07	0.04	2.99-3.15

Haemodynamic progression at 1 year

As regards the change in pulmonary vascular resistance (PVR), there is no statistical difference in absolute or proportional progression between groups 0, 1 and 2 (p=0.50 and p=0.55 by ANOVA respectively). However, there is a clear difference between groups 0, 1 and 2 combined and group 3 (p<0.0005 for absolute and proportional change).

Figure 6. Change in PVR in one year

	n=	Baseline PVR	1 year PVR	PVR change (abs)	P value (for comparison to baseline)	PVR change (%)
Group 0	10	162.6	179.4	16.8	0.43	11.4%
Group 1	8	197	279.7	82.7	0.07	40.6%
Group 2	34	295.5	363.0	67.5	0.02	24.3%
Group 3	92	754.5	593.5	-161.1	0.08	-13.2%

With regard to changes in mean pulmonary artery pressure, the absolute and proportional change in group 1 is not significantly different to that in group 0 (p=0.54 and p=0.46

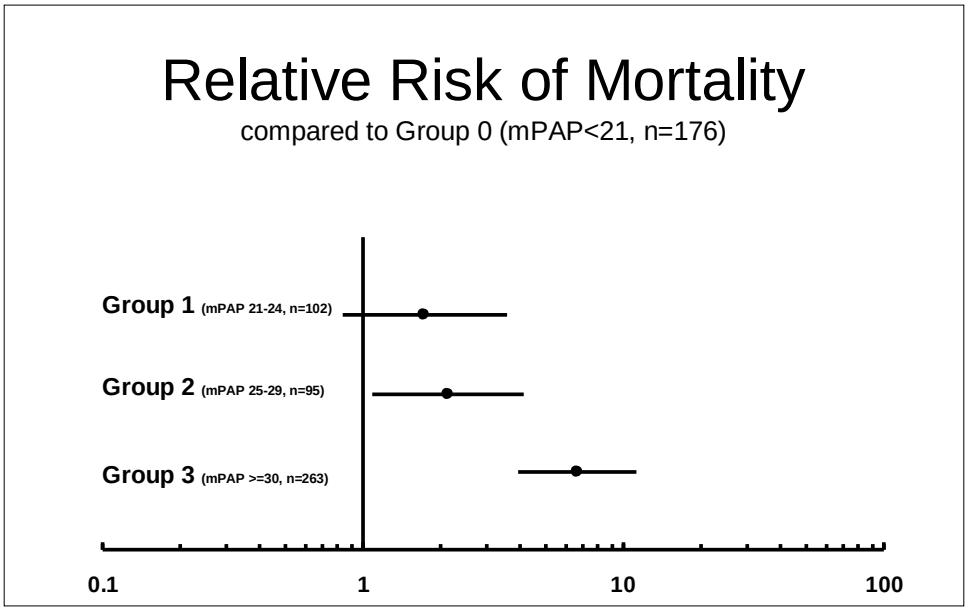
respectively). However, group 3 clearly is different to groups 0,1 and 2 combined (p=0.0003 and p=0.0008 respectively).

Figure 7. Change in mPAP in one year

	n=	Baseline mPAP	1 year mPAP	mPAP change (abs)	P value (for comparison to baseline)	mPAP change (%)
Group 0	11	18.4	33.5	+15.1	0.21	+81.6%
Group 1	9	21.9	29.1	+7.2	0.009	+32.6%
Group 2	35	26.7	30.1	+3.4	0.008	+12.7%
Group 3	99	45.0	42.9	-2.2	0.053	-3.5%

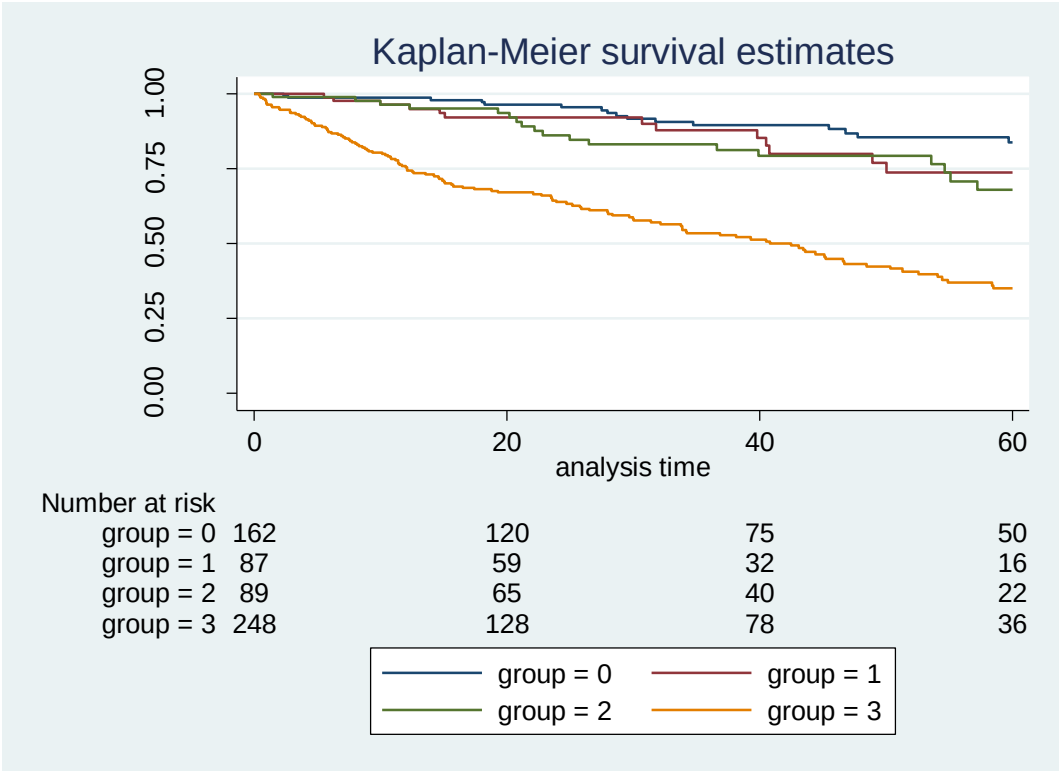
Survival

Unadjusted relative risk of survival compared to Group 0:

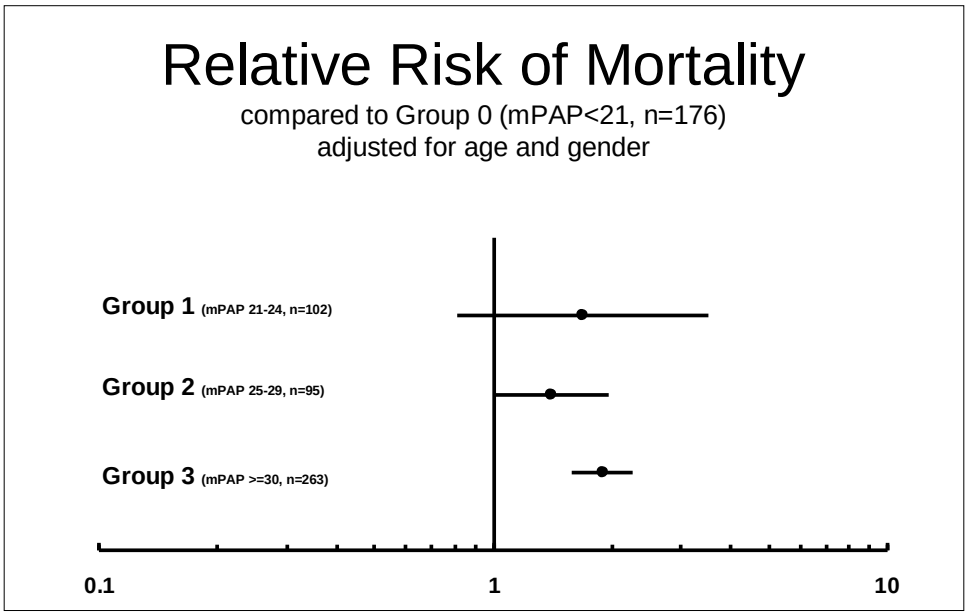


There is a clear trend towards worse survival in Group 1 than in Group 0 (p=0.15), and survival is clearly worse in group 2 than group 0 (p=0.03) and dramatically worse in group 3 than group 0 (p<0.0005).

In group 3, median survival is 42 months (95% CI for mean 31-48), in group 2 the median survival is 90 months (95% CI for mean starts at 64, upper limit not reached). 95% CI for median survival in group 0 is 101 months and in group 2 is 118 months. Median survival has not been reached in either group.



Survival adjusted for age and gender



Interestingly, after adjustment for age and gender, there was no trend at all to difference in survival between Group 1 and Group 2 (p=0.99). There is still a weak trend to worse survival in Group 1 compared to Group 0 (p=0.16) and a strong trend to worse survival in Group 2 compared to Group 0 (p=0.051). Survival in Group 3 remains clearly worse than in any other group. These findings suggest that the difference in age and gender across the groups may account for some of the differences in survival among groups 0, 1 and 2, and that the significance of borderline mPAP on survival should therefore be interpreted with caution.

Sensitivity analyses

Mean PVR in group 1 is 201.3. Survival is no worse in those in Group 1 with PVR≥200 than those with PVR <200 (HR 0.90, 95% CI 0.26,3.13). Those with high PVR have similar FVC % predicted to those with low PVR (p=0.79) but lower DLCO (62.3%, n=17 compared to 48.2%, n=24, p=0.004).

Patients in Group 1 with anticentromere antibodies have similar survival to those without after adjustment for age and gender (HR 1.38, 95% CI 0.14, 13.48).

Indicators of Progression to Pulmonary Hypertension

We compared baseline data in patients with systemic sclerosis who did not have pulmonary hypertension on initial right heart catheterisation (n=94) and who subsequently progressed to pulmonary hypertension (n=35) to those who did not progress (n=59). This shows that patients with higher pulmonary artery pressures and pulmonary vascular resistance are more likely to progress. Subgroup analysis is shown for patients without pulmonary fibrosis or raised pulmonary capillary wedge pressure at the time of initial right heart catheterisation (of whom 21 progressed and 33 did not).

Comparison of Mean baseline values in patients with systemic sclerosis without pulmonary hypertension on initial right heart catheterisation who do progress to pulmonary hypertension on subsequent right heart catheterisation to those who do not

	Patients who did not progress (n=59)	Patients who did Progress (n=35)	P value	P value in those without pulmonary fibrosis or raised wedge pressure
Age (years)	59.3 (56.0-62.6)	57.9 (54.2-61.5)	0.56	0.84
Gender	81.3% female	77.1% female	0.63	0.97
Body Surface area (m^2)	1.68 (1.63-1.73)	1.73 (1.66-1.79)	0.28	0.89
Functional class	2.4 (2.2-2.6)	2.3 (2.0-2.5)	0.48	0.50
Pulmonary fibrosis (prevalence)	40.4%	33.3%	0.51	N/A
Heart rate (bpm)	75.7 (71.4-79.9)	78.5 (73.5-83.5)	0.41	0.74
Right atrial pressure (mmHg)	5.0 (4.5-5.5)	4.7 (3.8-5.5)	0.47	0.85
Mean PA pressure (mmHg)	19.8 (19.0-20.5)	21.1 (20.2-22.0)	0.03	0.03
Pulmonary capillary wedge pressure (mmHg)	9.7 (9.0-10.4)	8.5 (7.4-9.6)	0.07	0.28
Pulmonary vascular	2.24 (2.00-2.48)	2.67 (2.43-2.92)	0.02	0.007

resistance (Wood units)				

Indicators of Progression to Pulmonary Hypertension

In patients without pulmonary hypertension on the initial RHC (groups 0 & 1), Cox proportional hazards analysis was performed to determine which variables are associated with progression to pulmonary hypertension within 5 years. Univariate analysis was performed in these 102 patients, and in the subset with SSc:

Univariate Cox Proportional Hazards analysis of association of variables with progression to pulmonary hypertension based on initial right heart catheterisation

Variable	Hazard ratio (95% CI)	P value in SSc patients
Age	0.99 (0.96-1.02)	0.57
Gender	0.71 (0.31-1.61)	0.41
Functional class	1.01 (0.60-1.72)	0.96
Subtype (diffuse=0, limited=1)	0.55 (0.23-1.29)	0.17
Body Surface area	6.53 (0.92-46.62)	0.06
Heart rate	1.03 (1.00-1.05)	0.03
Right atrial pressure	0.99 (0.82-1.20)	0.96
Systolic PA pressure	1.11 (1.03-1.21)	0.01
Diastolic PA pressure	1.16 (1.02-1.32)	0.03
Mean PA pressure	1.27 (1.07-1.51)	0.005
Cardiac output	1.14 (0.86-1.53)	0.36
Arterial saturation	1.00 (0.83-1.20)	1.00
PA saturation	0.99 (0.92-1.06)	0.71
Pulmonary vascular resistance (Wood units)	1.52 (1.01-2.30)	0.046
Pulmonary capillary wedge pressure	0.90 (0.77-1.05)	0.17

We found that age, gender, disease subtype (limited vs diffuse), baseline functional class,

presence of fibrosis, body surface area, heart rate, right atrial pressure, and cardiac output were poorly associated with progression to PH.

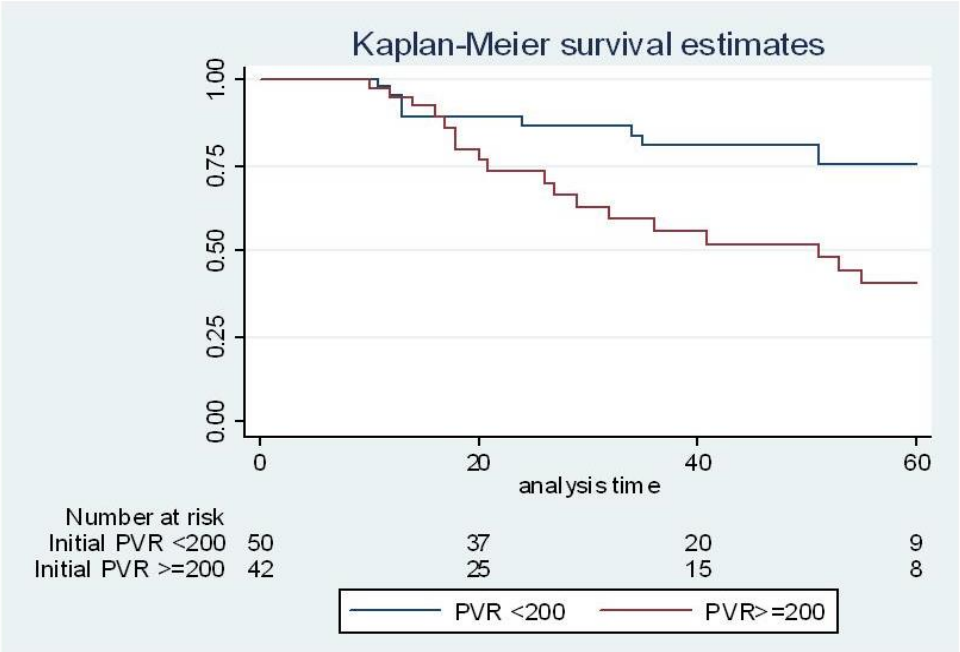
Higher mPAP (p=0.03) was associated with subsequent progression to pulmonary hypertension. Mean mPAP in patients who progressed to PH was higher than in patients who did not (21.1 vs 19.8, p=0.03).

Higher PVR also correlated strongly with progression to pulmonary hypertension (p=0.02).

These variables were looked at categorically. mPAP was taken as normal or borderline (mPAP≤20 or 21-24) and PVR as below or above mean (200 dynes.s.cm^{-5}). Presence of borderline mPAP (21-24) was associated with a trend towards progression to PH (odds ratio 2.0, 95% CI 0.9-4.7, p=0.11). The trend loses significance when adjusted for high PVR (p=0.48) while high PVR remains significant (odds ratio 3.1, p=0.02). High PVR is a particularly strongly associated with progression to PH amongst patients without lung fibrosis (OR 7.4, 95% CI 2.2-25.5, p=0.001).

Kaplan Meier analysis shows a clear divergence between those with PVR >200 and those <200 dynes.s.cm-5, (p=0.003 by log-rank test).

Kaplan-Meier survival analysis showing proportion of patients surviving without progression to PH categorized by baseline PVR (dynes.s.cm^{-5}).



Progression to PH over 5 years occured in 60% of those with baseline PVR ≥ 200 and 25% of those with baseline PVR under 200. High normal PVR was associated with an incidence rate ratio of 2.5 (95% CI 1.2-5.6) for development of PH within 5 years.

In order to understand these patient groups we looked further at other characteristics of the groups without pulmonary hypertension at baseline, categorised by PVR.

Furthermore, we looked at the distribution of normal and borderline values of both PVR and mPAP.

	PVR<200	**PVR>200**
mPAP < 20	149	47
mPAP 20-24	89	86

We then looked at differences between these two groups. We found that those with PVR > 200 were older, more frequently female, and had significantly more pulmonary fibrosis than those with lower PVR at baseline.

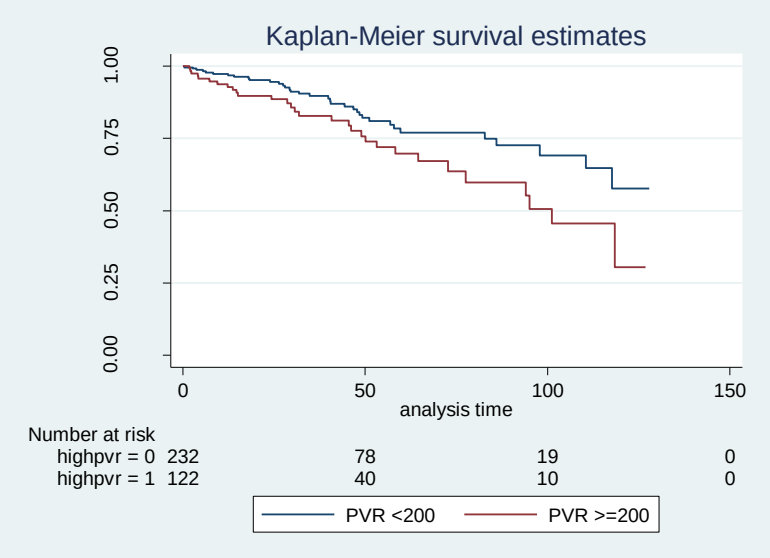
	PVR<200 (n=237)	PVR>200 (n=133)	P value
Age	56.1	62.3	<0.0001
Gender	17.6% Male	6.8% Male	0.0003
Systemic sclerosis	0.882	0.887	0.89
SSc subtype	75% limited	85% limited	0.06
Pulmonary Fibrosis	0.233	0.404	0.003
Functional class	2.4	2.5	0.29
mPAP	18.3	20.2	<0.0001
6MWD	339m (n=39)	327m (n=21)	0.71
NTproBNP	44 pmol/l (n=102)	68 pmol/l (n=42)	0.28
Echo PASP	30.4 (n=54)	32.2 (n=18)	0.39

Variables associated with Survival

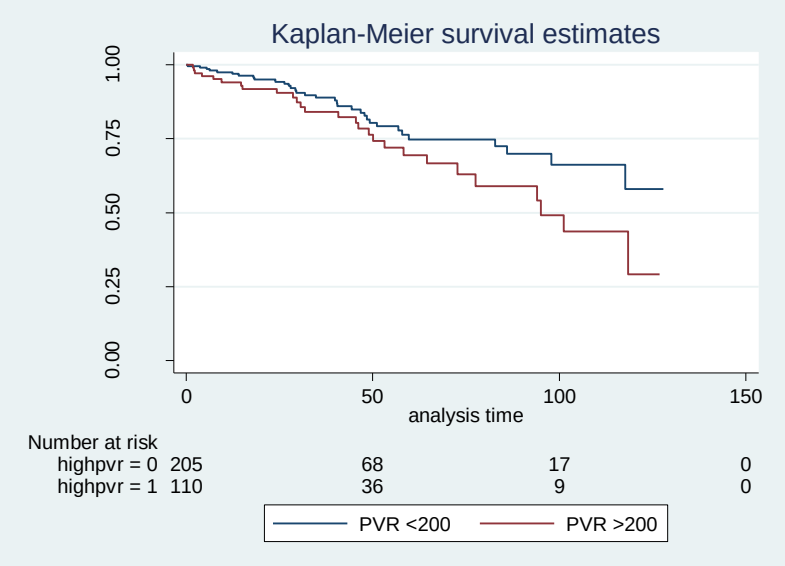
mPAP is not associated with survival on univariate analysis (p=0.16). In contrast, PVR is closely associated of survival. In analysis as a continuous variable each additional Wood Unit (1 wood unit = 80 dynes.s.cm^{-5}) is associated with a 61% increase in risk of mortality (HR 1.61 [1.30-2.00] p<0.0005). In analysis as a categorical variable as above (PVR ≥200 vs PVR <200) there is a similar additional risk of HR 1.62 [0.97-2.69], p=0.065 on Cox Proportional Hazard analysis.

We found a strong association between baseline PVR and survival, both for those patients with systemic sclerosis (p=0.06) and for all patients with connective tissue diseases (p=0.02).

Survival by PVR in all patients with connective tissue disease



Survival by PVR in all patients with systemic sclerosis



We tabulated the survival data to show the effect of baseline PVR out to 10 years in patients with connective tissue disease.

Years	Proportion alive if baseline PVR < 200	Proportion alive if baseline PVR ≥ 200
1 year	97.3% (95% CI 94-99)	93.8% (95% CI 87-97)
3 years	89.6% (95% CI 84-93)	82.8% (95% CI 73-89)
5 years	77% (95% CI 68-84)	69.6% (95% CI 57-79)
10 years	58.1% (95% CI 39-73)	30.4% (95% CI 8-57)

Subgroup analysis shows that in patients with pulmonary fibrosis (n=170), PVR does not predict survival (p=0.90), nor does mPAP predict survival (p=0.20).

3 Variable Model

Having completed these analyses of single variables we proceeded to formulating a multivariate model to predict progression to pulmonary hypertension. Variables which showed some significance on univariate analysis ($p<0.1$) were carried forward to multiple variable analysis. Pulmonary artery pressures lose significance and drop out. Body surface area, heart rate and pulmonary vascular resistance remain independently highly significant ($p\leq0.02$).

Using categorical variables, patients were classified as having above or below mean values of body surface area ($1.7m^2$), heart rate (77 beats per minute) and pulmonary vascular resistance (2.4 wood units, 192 dynes.s.cm^{-5}, which we rounded to 200 dynes.s.cm^{-5}). These mean values are between the mean of those patients who do and do not progress to pulmonary hypertension.

Cox proportional hazards analysis of indicators of progression to pulmonary hypertension

	Hazard ratio	Confidence intervals	P value
BSA ≥ 1.7m^2	3.82	1.53-9.53	0.004
Heart rate ≥ 77 bpm	3.54	1.52-8.24	0.003
PVR > 2.5 Wood units (200 dynes.s.cm^{-5})	3.56	1.49-8.49	0.004

There is no interaction between these three variables. If body surface area is removed from the analysis the significance of the association with heart rate and PVR drop (to p=0.009 and p=0.017 respectively). Patients with BSA ≥ 1.7m^2 have a similar heart rate to those with BSA <1.7 m^2 (81.8 vs. 81.1, p=0.65). Patients with BSA ≥ 1.7m^2 have a lower PVR than those with BSA <1.7 m^2 (5.2 vs. 6.3 wood units, p=0.025). Patients with heart rate ≥77 beats per minute have a significantly higher PVR than patients with a heart rate < 77 beats per minute (6.6 vs. 4.2 wood units, p=0.0001).

A simple combined score was derived:

Scoring system for likelihood of progression to pulmonary hypertension in future based on initial right heart catheterisation in patients with systemic sclerosis

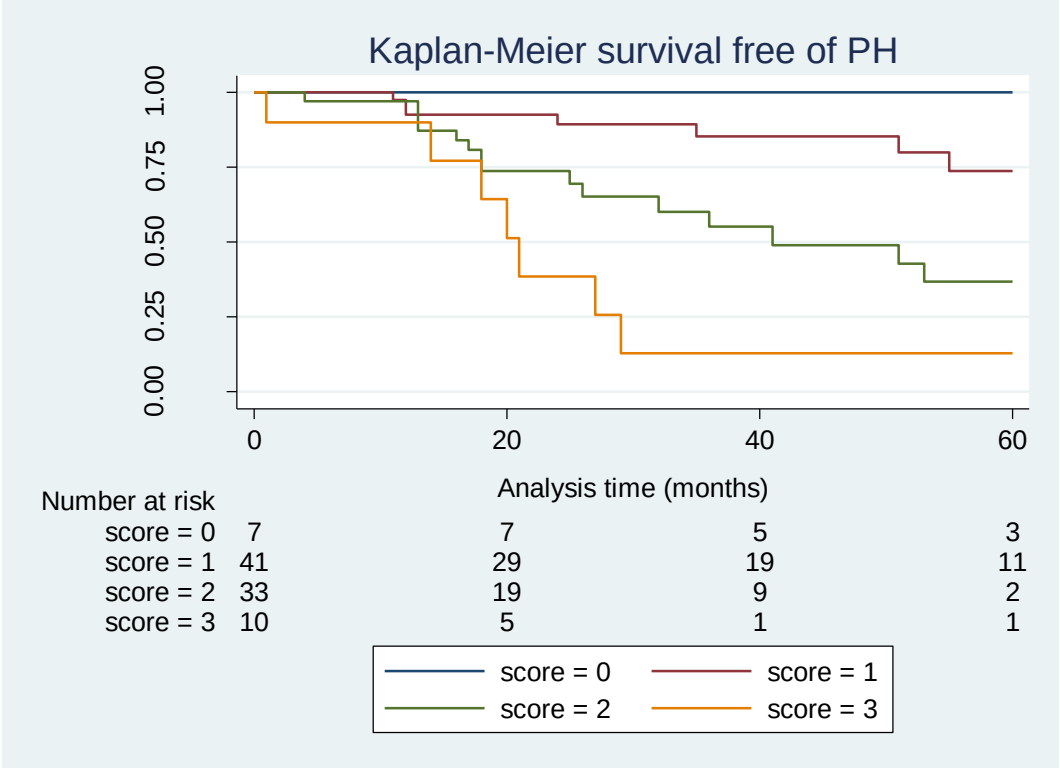
	0	**1**
Body surface area	< $1.7m^2$	≥ $1.7m^2$
Heart rate	< 77 bpm	≥ 77 bpm
Pulmonary vascular resistance	<2.5 wood units (<200 dynes.s.cm^{-5})	≥ 2.5 wood units (≥ 200 dynes.s.cm^{-5})

Distribution of scores in our patient cohort and the prevalence of progression at 3 years by initial score

Score	**Number of patients**	**3 year progression (%)**
0	7	0%
1	41	15%
2	33	40%
3	10	87%

There was no statistically significant difference detected between score 0 (n=7) and score 1 (n=31), p=0.22 by log-rank, but there was a clear difference between score 1 (n=41) and score 2 (n=33), p=0.007 by log-rank, and between score 2 (n=33) and score 3 (n=10), p=0.03 by log-rank.

Kaplan-meier survival analysis of patients with systemic sclerosis who do not have pulmonary hypertension on initial right heart catheterisation. the progression to pulmonary hypertension over time is shown stratified by a score which is a composite of 3 categorical variables based on body surface area, heart rate and pulmonary vascular resistance.



Discussion

In this study we explored how to interpret the findings in patients with systemic sclerosis who are subjected to right heart catheterisations and found not to have pulmonary hypertension. We have shown that patients with PVR above 200 dynes.s.cm^{-5} are 2.5 times as likely to progress to pulmonary hypertension and 2.2 times as likely not to survive over the subsequent five years.

This finding has important implications. Firstly, it suggests that patients with higher PVR should have closer follow up, with consideration being given to repeat right heart catheterisation in these patients. Additionally, this may identify a group of patients who may ultimately benefit from prophylactic treatment. This is an unproven concept, but one which could be tested in a clinical trial as there is a well-defined high risk group.

Further, we have shown that in patients with systemic sclerosis who do not have pulmonary hypertension, a simple score based on body surface area, heart rate and pulmonary vascular resistance is useful in stratifying patients by the risk of future progression to pulmonary hypertension.

This analysis is open to criticisms. Our group of patients were selected for repeat right heart catheterisation due to clinical concern. The rate of progression calculated in our cohort may therefore be higher than would be the case in a population not selected for repeated right heart catheterisation.

The finding that higher body surface area is associated with a higher risk of progression to pulmonary hypertension is novel and requires explanation. The significance of the association was much higher on multiple variable analysis than on single variable analysis. And there may be complex interactions between the variables which we cannot unpick. We have separately looked at the association between body surface area and survival in patients with pulmonary hypertension (see also page 67). Although patients with a larger body surface area tend to have a lower pulmonary vascular resistance, after adjustment for pulmonary vascular resistance a larger body surface area is associated with a higher risk of progression. This is a novel finding and will require validation in independent cohorts.

Chapter 4. Raised body mass index is associated with increased prevalence of connective tissue disease associated pulmonary hypertension and improved survival

Schreiber BE, Dobarro D, Handler C, Keir G, Wells AU, Denton CP, Coghlan JG. Poster presentation, British Society of Rheumatology Annual Conference, Glasgow, 2012.

Abstract

Objectives

It is not known whether obesity is associated with pulmonary hypertension in patients with connective tissue disease, nor whether it is a predictor of survival.

Methods

We performed a retrospective analysis of 417 patients with connective tissue disease who underwent right heart catheterization and pulmonary function testing. We explored the association of body mass index to the diagnosis on right heart catheterization and whether survival in patients with pulmonary hypertension was associated with obesity (BMI>30kg/m2).

Results

Post-capillary pulmonary hypertension was diagnosed in 15% of obese patients and in 8% of non-obese patients (p=0.048). The incidence of pulmonary arterial hypertension did not differ. Obese patients had worse functional class, higher right atrial and pulmonary capillary wedge

pressures, higher cardiac output and tended to have higher mean pulmonary artery pressures (31.8 mmHg compared to 29.9 mmHg, p=0.052).

Amongst patients with pulmonary hypertension, survival was significantly better in obese patients (hazard ratio 0.47, p=0.020, 95% CI 0.25,0.89). Amongst patients with pulmonary arterial hypertension, a trend to improved survival was still seen in obese patients.

Conclusions

In a pulmonary hypertension centre, obese patients selected for right heart catheterization were more likely to have pulmonary hypertension, particularly post-capillary pulmonary hypertension. However, survival in obese patients with pulmonary hypertension is overall better than survival in non-obese patients. Further work is required to better understand the underlying reasons for these associations.

Introduction

Obesity is known to impact on heart and lung disease, but its role in pulmonary hypertension has not been clarified. Using a large clinical cohort of patients with connective tissue disease referred to a pulmonary hypertension service, we investigated the relationship between BMI (body mass index) and cardiopulmonary findings, including lung function tests and pulmonary haemodynamics. We explored whether obesity was associated with an increased prevalence of pulmonary hypertension. Lastly, we researched the association between obesity and survival in patients with confirmed pulmonary arterial hypertension.

Methods and Materials

We retrospectively reviewed a prospectively collected single centre database of patients with connective tissue disease who were assessed in a regional Pulmonary Hypertension centre with right heart catheterisation between January 1999 and April 2010.

The patients underwent assessment with lung function tests within three months of a diagnostic right heart catheterisation. Heart rate, systolic and diastolic blood pressure and oxygen saturation were recorded at the time of right heart catheterisation. At right heart catheterisation, right atrial pressure, pulmonary artery pressures and pulmonary capillary wedge pressure were recorded by Swan-Ganz catheter. The zero position was taken as the midpoint between the sternum and the spine. Left ventricular end diastolic pressure was measured if a reliable pulmonary capillary wedge tracing could not be obtained and if necessary to confirm elevated wedge pressures. Where left ventricular end diastolic pressure was used this was treated as equivalent to pulmonary capillary wedge pressure. Cardiac output was computed by repeated thermodilution, with three consecutive calculations within 10%.

Weight, height and smoking status were recorded at the time of the pulmonary function test, which was performed within three months of the diagnostic right heart catheterisation. Data on baseline pulmonary function tests, weight and height were available for 417 of 1001 patients

and these patients were included in the analysis. Survival data was obtained from the National Health Service database in April 2010.

Statistical analysis was performed using Stata® (StataCorp LP, Texas) version 10.0. Distribution of variables was assessed graphically. The distribution of variables was assessed graphically. Normally distributed variables were compared using t-test, non-parametric variables were compared using the Mann-Whitney test, and categorical variables using Chi squared. Kaplan-Meier curves were used for survival analysis, with the log-rank test for comparing survival between groups.

Results

Of the 417 patients, 79 (18.9%) were obese (BMI≥30) and 338 (81%) were not. Only 5 patients had BMI>40. The distribution of BMI in the 417 patients is shown in Figure 1, and baseline characteristics in Table 1.

Figure 1. Distribution of body mass index in the 417 patients

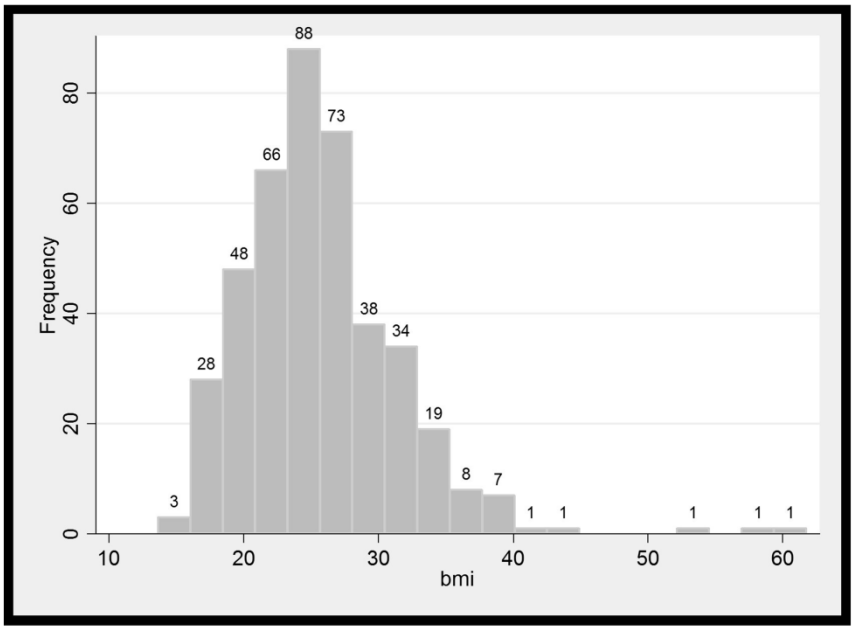


Figure 1

Table 1. Comparison of baseline characteristics between obese and non-obese patients

	Not obese (BMI<30) n=338	**Obese (BMI≥30) n=79**	**Significance of difference (p value)**
Age	58.8	55.8	0.049
Gender	20.1%	15.1%	0.318*
SSc Diagnosis	89.6%	82.2%	0.067*
Functional class (I/II/III/IV)	14/80/157/39 Mean 2.76	0/10/50/8 Mean 2.97	0.014*
Six minute walking distance	268.2m n=130	266.9 n=35	0.956
FVC (litres)	2.38 (0.86)	2.17 (0.82)	0.047
FVC % predicted	81.4%	75.7%	0.076
FEV1 % predicted	74.7% (21.9)	69.2% (19.1)	0.041
FEV1/FVC	0.78 (0.11)	0.78 (0.10)	0.971
Proportion with FEV1/FVC <70% pred	21.5%	21.8%	0.951
DLCO % predicted	43.5% (16.5)	45.9% (18.0)	0.270
Smoker (never/past/current)	198/114/14	42/29/3	0.857*
Heart rate	82.0 (15.0)	82.8 (16.2)	0.66
Systolic BP	137.6 (25.9)	137.9 (24.5)	0.936
Diastolic BP	73.4 (12.1)	76.3 (13.4)	0.068
RA pressure	6.8 (5.2)	7.5 (3.8)	0.010
PA systolic pressure	48.2 (21.3)	49.8 (18.7)	0.017+

PA diastolic pressure	17.7 (9.0)	19.2 (7.4)	0.029+
PA mean pressure	29.9 (13.0)	31.8 (11.5)	0.052+
Proportion with PH (mPAP≥25)	56.8% (n=338)	73.4% (n=79)	0.007
Proportion with precapillary PH (mPAP≥25 and PCWP≤15)	48.8%	58.2%	0.132
Proportion with post-capillary PH (mPAP≥25, PCWP>15)	8.0%	15.2%	0.048
Proportion with PAH (mPAP≥25, PCWP>15, FVC≥70% pred)	29.5%	35.1%	0.345
Cardiac output	4.5 l/min (1.4)	5.3 l/min (1.2)	<0.0005
Cardiac index	2.67 (0.77)	2.71 (0.78)	0.705
Oxygen saturation	94.9% (4.2) n=320	96.0% (2.9) n=76	0.010+
PVR	410.2 (393.3) n=333	323.8 (241.9) n=74	0.212+
Pulmonary capillary wedge pressure	10.1 (4.5) n=335	12.3 (4.3) n=79	0.0002

* by Chi Squared, + by Mann-Whitney test

We compared the baseline characteristics of patients with obesity (mean BMI 34.5) to patients without (mean BMI 23.6).

Cardiac output, aortic pressures was normally distributed. However, right atrial pressure, systolic, diastolic and mean pulmonary artery pressures and pulmonary vascular resistance were not.

We found that compared with non-obese patients, obese patients were three years younger and had slightly worse functional class. There was a trend towards a lower proportion of scleroderma in obese patients than in non-obese patients.

On pulmonary function tests, the forced lung capacity was 200 millilitres less on average in obese patients than in non-obese patients, but there was no association with obstructive spirometry. There was no significant difference in smoking history.

Heart rate and systolic blood pressure were similar, but there was a trend towards a 3mm higher diastolic pressure in obese patients. Right heart catheterisation showed slightly higher right atrial pressures in obese patients, and almost twice the incidence of post-capillary pulmonary hypertension (15% compared to 8% in this cohort). Pulmonary capillary wedge pressures were 2 mmHg higher in obese patients on average. Cardiac output was slightly higher but cardiac index was similar. Oxygen saturation was slightly higher in obese patients.

Amongst 123 patients with pulmonary arterial hypertension (precapillary pulmonary hypertension and forced vital capacity>70%), mean pulmonary artery pressure was 38.4 mmHg and mean pulmonary vascular resistance was 557 dynes.s.cm^{-5}. There was no significant difference between obese and non-obese patients in mean pulmonary artery pressure (p=0.68), right atrial pressure (p=0.81) or trans-pulmonary gradient (p=0.91). Cardiac output was higher in obese patients (5.3 vs 4.4 litres/minute, p=0.002) and there was a trend to lower pulmonary vascular resistance in obese patients (460 vs 584 dynes.s.cm^{-5}, p=0.10).

Outcomes

5 year survival data was analysed. In the cohort as a whole median survival was 71.6 months. There was no difference in survival between obese and non-obese patients (p=0.267).

Figure 2. Kaplan-Meier survival curve in obese and non-obese patients

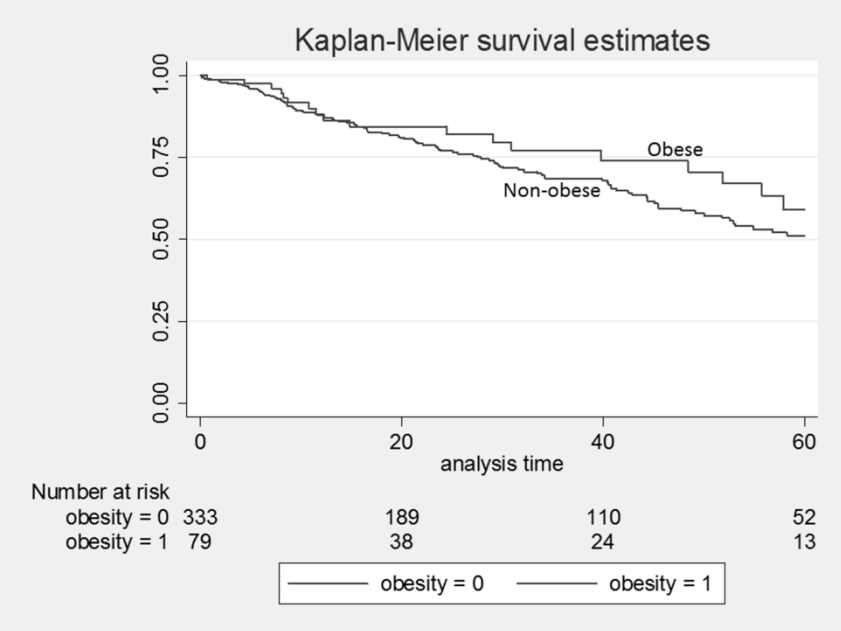


Figure 2

Amongst patients with pulmonary hypertension (n=210) distribution of weights in patients was as follows: 12 patients were underweight (5.7%), 81 patients were of normal weight (38.4), 72 were overweight (34.1%), 31 were class I obese (14.7%), 10 were class II obese (4.7%) and 5 were class III obese (2.4%). The mean BMI in patients with pulmonary hypertension was higher than in patients without (26.4 vs 24.9, p=0.007).

There was better outcome in obese patients (p=0.017 by log-rank). 3 year survival was 51.9% (95% CI 42.4,61.0) in non-obese patients but 71.3% (95% CI 52.4,83.8) in obese patients. On cox proportional hazards analysis, obesity was associated with a hazard ratio of 0.47 (p=0.020, 95% CI 0.25,0.89). This difference persists after adjustment for age and gender. After adjustment for mean pulmonary artery pressure and cardiac output hazard ratio for obesity is

0.58, p=0.010. With adjustment for pulmonary capillary wedge pressure, the hazard ratio for obesity is 0.61, p=0.09.

If the analysis is restricted to patients with pulmonary arterial hypertension (mPAP ≥ 25, PCWP ≤ 15, FVC > 70% predicted) there is still a trend to better survival (n=123, hazard ratio 0.44, p=0.12, 95% CI 0.16, 1.24).

The improved survival in obese patients with pulmonary hypertension compared to non-obese patients holds true even when patients who are underweight (BMI<18.5) or class III obese (BMI>40) are excluded from the analysis. Survival is better in patients with class I or class II obesity than in patients who are of normal weight or overweight (hazard ratio 0.47, p=0.025, 95% CI 0.24,0.91).

Compared to patients with class I obesity (BMI 30.0-34.9), underweight patients' hazard ratio for mortality is 2.29 (p=0.179, 95% CI 0.68,7.69); patients of normal weight have a hazard ratio for mortality of 2.37 (p=0.026, 95% CI 1.11,5.08); patients with class II obesity (BMI 35.0-39.9) have a hazard ratio of 1.13 (p=0.878, 95% CI 0.24,5.38) and those with class III obesity (BMI ≥40.0) have a hazard ratio of 1.16 (p=0.888, 95% CI 0.14,9.34).

Figure 3. Kaplan-Meier survival curve for patients with pulmonary arterial hypertension

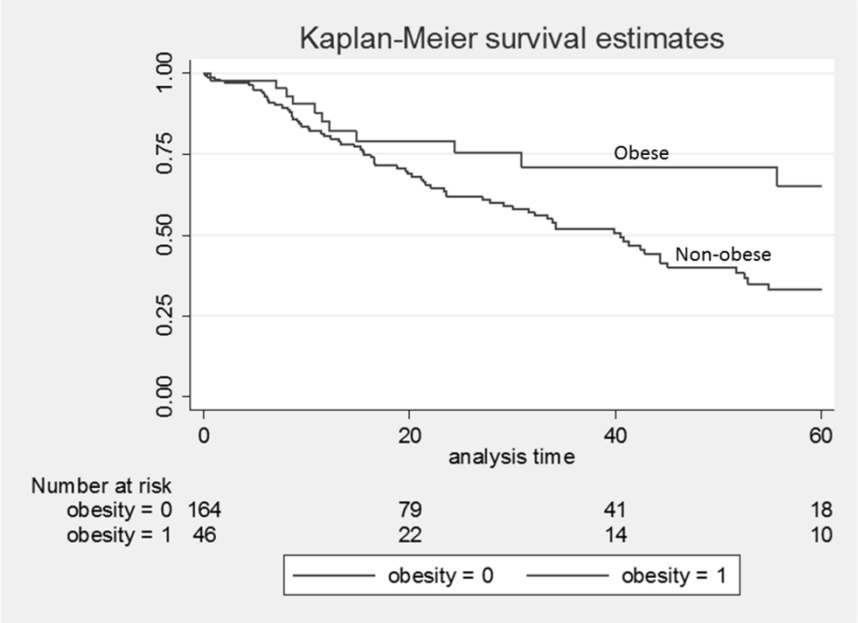


Figure 3

Among patients without pulmonary hypertension, there was no difference in survival between obese and non-obese patients (p=0.52).

Discussion

In our cohort of 417 patients with connective tissue disease, 19% were obese. Obese patients were on average 3 years younger than non-obese patients. They reported slightly more functional limitation, and the forced lung capacity was about 200ml smaller than non-obese patients. There was no association between obesity and smoking or systemic hypertension in our patients.

Right heart catheterisation revealed some subtle changes associated with obesity. These included higher right atrial pressure (by 0.7 mmHg), slightly higher systolic and diastolic pulmonary artery pressures (by about 1.5 mm Hg) and higher average pulmonary capillary wedge pressure (by 2.2 mmHg). Cardiac output was higher by 0.8 litres/minute although cardiac index was similar in the two groups. Consequently post-capillary pulmonary hypertension was more frequently diagnosed amongst obese patients.

The higher wedge pressures in patients with obesity may reflect changes in left ventricular function related to obesity. Obesity is associated with subclinical left ventricular impairment of diastolic, and perhaps also systolic dysfunction.[32] Furthermore, cardiac catheterisations performed in 10 asymptomatic obese volunteers showed raised wedge pressure and pulmonary artery pressures.[33] However, determining the zero position in the body is more difficult in obese patients and this may partly explain the higher values.

Consequently, post-capillary pulmonary hypertension was diagnosed in 15% of obese patients compared to 8% of non-obese patients. There was no significant difference in the incidence of pre-capillary pulmonary hypertension or pulmonary arterial hypertension using forced vital capacity>70% predicted to exclude significant lung disease.

Our finding that there is no association between obesity and the prevalence of pulmonary arterial hypertension is in agreement with previous studies. A retrospective review of 401 patients in the pulmonary hypertension (PH) database of Mayo Clinic in Florida found no correlation between BMI and diagnosis of PH when these patients were compared with controls (n=578).[34] Burger and colleagues compared the distribution of body mass index in patients with pulmonary arterial hypertension from the REVEAL registry with age- and sex-matched controls in the National Health and Nutrition Examination Survey database. They found no difference in mean BMI overall. There was a higher proportion at either end of the weight spectrum which was attributable to the characteristics of specific subgroups: idiopathic pulmonary arterial hypertension and drugs and toxins associated pulmonary arterial hypertension subgroups had a higher percentage of obese patients compared with controls, whereas congenital heart disease and connective tissue disease associated pulmonary arterial hypertension subgroups had a higher percentage of underweight patients.[35]

Our finding that obese patients with pulmonary hypertension had half the mortality of non-obese patients is intriguing. To our knowledge, this has not been reported before. There have been reports of obesity as a protective factor in left heart failure. Among the 7599 patients in the

Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program, patients with BMI<30 kg/m^2 had higher mortality than patients with BMI>30 kg/m^2.[36] This has been shown in other groups of patients with systolic heart failure, and has been called the 'obesity paradox'.[37, 38, 39] It has been suggested that the adaptive morphological and functional cardiac changes in obesity may be protective, or that the adipose tissue itself, especially perivascular and epicardial fat, may be metabolically active and perhaps protective.[40] It has previously been suggested that this may be due to higher mortality in cachexic patients due to severe cardiac or non-cardiac disease in the non-obese group. However, we have shown a clear mortality benefit even when underweight patients were excluded from the analysis.

It is possible that the higher capillary wedge pressures in patients with obesity reflect a greater incidence of post-capillary pulmonary hypertension even in patients with pulmonary capillary wedge pressure ≤ 15mmHg. We cannot exclude technical issues such as difficulty in deciding on the zero point which may tend to overestimation of pressures in larger patients.

It is not clear whether the relationship between weight and pulmonary haemodynamics is different in patients with connective tissue disease. The REVEAL registry found that while patients with idiopathic pulmonary arterial hypertension have a higher BMI than the control group (29.1 vs 28.1, p<0.001), those with connective tissue disease associated pulmonary arterial hypertension have a lower BMI than controls (27.6 vs 28.7, p<0.001). Whether these small differences are due to comorbidities in connective tissue disease such as gastrointestinal involvement is unknown.

Strengths of the study include the large cohort of connective tissue disease patients, the thorough investigation with pulmonary function tests and right heart catheterization and complete survival data. Our study has important limitations. Principally, that it is retrospective and there are incomplete data, especially pulmonary function tests. This finding would need to be replicated in a larger prospective cohort.

In summary, in patients with connective tissue disease obesity is associated with changes in pulmonary function tests and pulmonary haemodynamics. Obese patients are not more likely to be diagnosed with pulmonary arterial hypertension, but post-capillary pulmonary hypertension appears to be more prevalent. Obese patients with pulmonary hypertension have longer survival overall than non-obese patients, and a trend is seen to longer survival even when patients with lung disease or post-capillary pulmonary hypertension are excluded. The underlying reasons for this are not clear, and further prospective studies would be helpful in clarifying the role of obesity in the diagnosis and prognosis of pulmonary hypertension.

Chapter 5. Diagnosis and prognosis of pulmonary arterial hypertension in systemic lupus erythematosus and systemic sclerosis

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Oral presentation at Annual Scientific Meeting of the British Society of Rheumatology, Brighton, April 201

Winner of Young Investigator Award

Abstract

Background

PAH is less commonly associated with SLE than with SSc. Previous work has suggested that survival is better in SLE-PAH but it is not clear if this is because the disease is milder or there is a better response to therapy.

Methods

Single centre retrospective analysis of diagnostic right heart catheterisations performed in patients with SSc or SLE. We have analysed baseline parameters, response to treatment at follow up right heart catheter and survival. PAH was defined as mPAP≥25 mmHg, PCWP≤15 mmHg, PVR ≥3 WU and FVC predicted (where available) ≥70%.

Results

Patients with SLE-PAH are younger (n=21, mean 43.9 yrs) than patients with SSc-PAH (n=309, mean 60.7 yrs, p<0.00005 for comparison). Both patient groups were predominantly female (95.5% in SLE-PAH, 84.5% in SSc-PAH, p=0.16).

Patients with SLE-PAH had higher mean mPAP than patients with SSc-PAH (47.0 and 41.0 mmHg respectively, p=0.03 for comparison). PVR was similar (means of 780 and 689 respectively, p=0.31). NT-pro-BNP values were also similar (SLE-PAH: n=9, mean 220 pmol/l. SSC-PAH: n=117, mean 248, p=0.84 for comparison).

Pulmonary function tests showed a lower FVC % predicted in SLE-PAH (n=8, mean 81.4%) compared to SSc-PAH (n=157, mean 94.7%, p=0.03 for comparison). Nonetheless DL_{CO} % predicted was lower in the SSc-PAH patients (SLE-PH: n=8, mean 52.7%. SSc-PH: n=139, mean 38.6%, p=0.0012 for comparison). WHO Functional class was similar in the two groups (mean 3.0 in SLE-PAH vs 3.1 in SSc-PAH, p=0.93). Six minute walking distance was on average 54 metres further in the SLE-PAH group (SLE-PAH: n=17, mean 301. SSc-PAH: n=178, mean 247, p=0.08 for comparison)

However, survival is clearly better in SLE-PAH compared to SSC-PAH (log-rank test p=0.02). Median survival is 39.9 months in the SSc-PAH group (95% CI 30.9-45.2). Median survival was not reached in the SLE-PAH cohort, but the 95% confidence interval for the median survival starts at 76.8 months. 1 year survival is 81.4% (58-93) in SLE-PAH compared to 79.5% (74-84) in SSc-PAH. 5 year survival is 76% (95% CI 51-89) in the SLE-PAH cohort and 32.8% in the SSc-PAH cohort (95% CI 26-40).

	SLE-PAH (n=22)	SSc-PAH (n=309)
1 year	81.4% (58-93)	79.5% (74-84)
3 year	76% (51-89)	52.7% (46-59)
5 year	76% (51-89)	32.8% (26-40)

Follow up catheterisation showed significantly more improvement in mPAP (-5.7 vs =0.6, p=0.01) and in PVR (-228 vs -38, p=0.006). A larger proportion showed any improvement in PVR in the SLE-PAH cohort (88% vs 62%, p=0.03).

Cox proportional hazards analysis shows that underlying diagnosis (SLE vs SSc) is not a significant predictor of mortality after adjustment for age, baseline haemodynamics, and DL_{CO}.

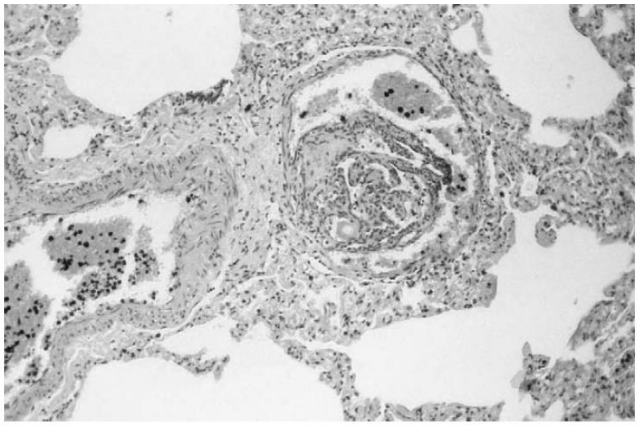
Conclusion

Compared to patients with SSc-PAH, patients with SLE-PAH are younger and have higher DLco % predicted. Intial pulmonary artery pressures are higher but haemodynamic responses to therapy in SLE-PAH are of greater magnitude and seen more frequently. These differences may account for the markedly better survival in patients with SLE-PAH.

Introduction

Sir William Osler was the first to recognize that SLE may be associated with pulmonary complications.[41] A post-mortem study of 90 patients with SLE associated pulmonary involvement included 4 patients with PH. Each of these patients had plexiform lesions (figure 1).[42] A number of the studies have used an unsatisfactory echocardiographic definition of pulmonary hypertension (e.g. Echo derived right ventricular systolic pressure greater than 30mmHg).[43,44]

Figure 1. Image of lung specimen from post-mortem study showing plexiform arteriopathy with organizing thrombosis in a patient with systemic lupus erythematosus.



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Why should SLE be different?

There are several possible causes of pulmonary hypertension in SLE, including recurrent thromboemboli, particularly in patients with antiphospholipid antibodies, pulmonary vasculitis, interstitial lung disease, left ventricular disease as well as pulmonary arterial hypertension similar to idiopathic PAH. There is some evidence that endothelin levels are elevated in patients with SLE and this may contribute to PAH.[45]

Pulmonary hypertension in SLE is associated with active disease and with many other major organ complications. Patients with SLE and suspected PAH require investigations to exclude interstitial lung disease and pulmonary thromboembolic disease. Thromboembolic disease is certainly more common in patients with SLE and is a common finding at post-mortem,[46] and the

presence of lupus anticoagulant or antiphospholipid antibodies is associated with a more than 4 fold increase in the risk of chronic thromboembolic pulmonary hypertension.[47]

There may be an important role for immunosuppression with cyclophosphamide and prednisolone in the treatment of PAH associated with SLE and MCTD. A small Mexican randomised open label study comparing cyclophosphamide to enalapril found a treatment benefit in terms of haemodynamic improvement and functional class improvement.[48] A small French retrospective case series suggested that half of patients with SLE or MCTD and PAH respond to immunosuppression with steroids and monthly intravenous cyclophosphamide, especially those with functional class I or II.[49,50]

Only a few patients with SLE-PAH have been included in the clinical trials of advanced therapies for pulmonary hypertension, although Bosentan was found to be helpful in a small case series.[51] However, guidelines suggest patients with CTD-PAH should be treated in the same way as IPAH.[14]

Data from baseline characteristics of the REVEAL cohort has recently been published.[52] All newly and previously diagnosed patients with World Health Organization (WHO) group 1 PAH meeting RHC criteria at 54 US centers were consecutively enrolled. The inclusion criteria are mPAP > 25 mmHg or >30 mmHg with exercise, PCWP <18 mmHg and pulmonary vascular resistance of > 240 dynes.s.cm^{-5}. For this study, patients with PCWP >15 were excluded, as were those with severe lung fibrosis on HRCT or with moderate lung fibrosis on HRCT and total lung capacity < 60% predicted. They found several differences between IPAH and CTD-PAH patients. CTD-PAH patients were older, more frequently female and less obese. They had lower pulmonary artery pressures and higher cardiac outputs, lower six minute walking distances and higher NT-pro-BNP levels. They more frequently had mild ILD on HRCT and had lower DLco % predicted. One year survival was lower in CTD-PAH patients (86% vs 93%, $p<0.0001$).

Among patients with CTD-PAH and a defined CTD diagnosis, 399 had SSc, 110 had SLE, 52 had MCTD and 28 had RA. Comparing SSc-PAH to SLE-PAH, age was different (61.8 ± 11.1 years vs 45.5 ± 11.9 respectively, p<0.0001). There was a clear difference in race (The majority of patients with SSc-APAH were white (84%); in contrast, only 37% of patients with lupus were white, 32% were African American, 18% were Hispanic, and 13% were of another racial background). Raynaud's phenomenon and renal insufficiency were more common in SSc-PAH patients.

Treatments differed, with more endothelin receptor antagonists used in SSc-PAH than SLE-PAH, and more immune suppressants in SLE-PAH than in SSc-PAH. At 1 year from the time of enrollment, 82% of the patients with SSc-PAH were alive, compared with 94% of the patients with SLE-PAH (p<0.0009).

Results from the reveal registry: comparison of pulmonary arterial hypertension associated with systemic sclerosis and systemic lupus erythematosus

	SSc associated PAH	SLE associated PAH	P value
FC III/IV	74.8	69.8	Not sig.
Mean PA pressure	44.6	46.6	Not sig.
Pulmonary Vascular Resistance	9.6	10.7	0.056
6 min walk distance	288	324	0.12
NTproBNP (pg/ml)	2893	740	0.01
DLCO % predicted	41.2	53.3	<0.0001

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The prognosis of patients with SLE-PAH appears to be intermediate between idiopathic PAH and SSc associated PAH. In the UK national pulmonary hypertension data, 1 and 3 year survival in the 28 patients with SLE-PAH were 78% and 74% respectively. Of patients with SLE 75% were treated with advanced therapy whereas 86% received immunosuppression.[53] This study also found that although haemodynamics were similar in SLE and SSc, survival was better in SLE.

PAH is less commonly associated with SLE than with SSc. Previous work has suggested that survival is better in SLE-PAH but it is not clear if this is because the disease is milder or there is a better response to therapy.

Methods

Single centre retrospective analysis of diagnostic right heart catheterisations performed in patients with SSc or SLE. We have analysed baseline parameters, response to treatment at follow up right heart catheter and survival. PAH was defined as mPAP≥25 mmHg, PCWP≤15 mmHg, PVR ≥3 WU and FVC predicted (where available) ≥70%.

Results

Table 1. Baseline characteristics in patients with SLE-PAH and SSc-PAH.

	SLE-PAH n=21	SSc-PAH n=234	p value
Age	46.2	60.3	<0.00005
Male	9.5%	15.8%	0.45
mPAP	45.9	40.5	0.08
PVR	747	659 (n=233)	0.43
NTproBNP	220 (n=9)	248 (n=117)	0.84
FVC % predicted	82.9% (n=7)	96.3% (n=103)	0.036
DLCO % predicted	53.1% (n=7)	41.6% (n=108)	0.02
Functional Class	3.0	3.0 (n=231)	0.56
Six minute walking distance	309 (n=17)	265 (n=132)	0.16

Patients with SLE-PAH are younger (n=21, mean 43.9 yrs) than patients with SSc-PAH (n=309, mean 60.7 yrs, p<0.00005 for comparison). Both patient groups were predominantly female (95.5% in SLE-PAH, 84.5% in SSc-PAH, p=0.16).

Patients with SLE-PAH had higher mean mPAP than patients with SSc-PAH (47.0 and 41.0 mmHg respectively, p=0.03 for comparison). PVR was similar (means of 780 and 689

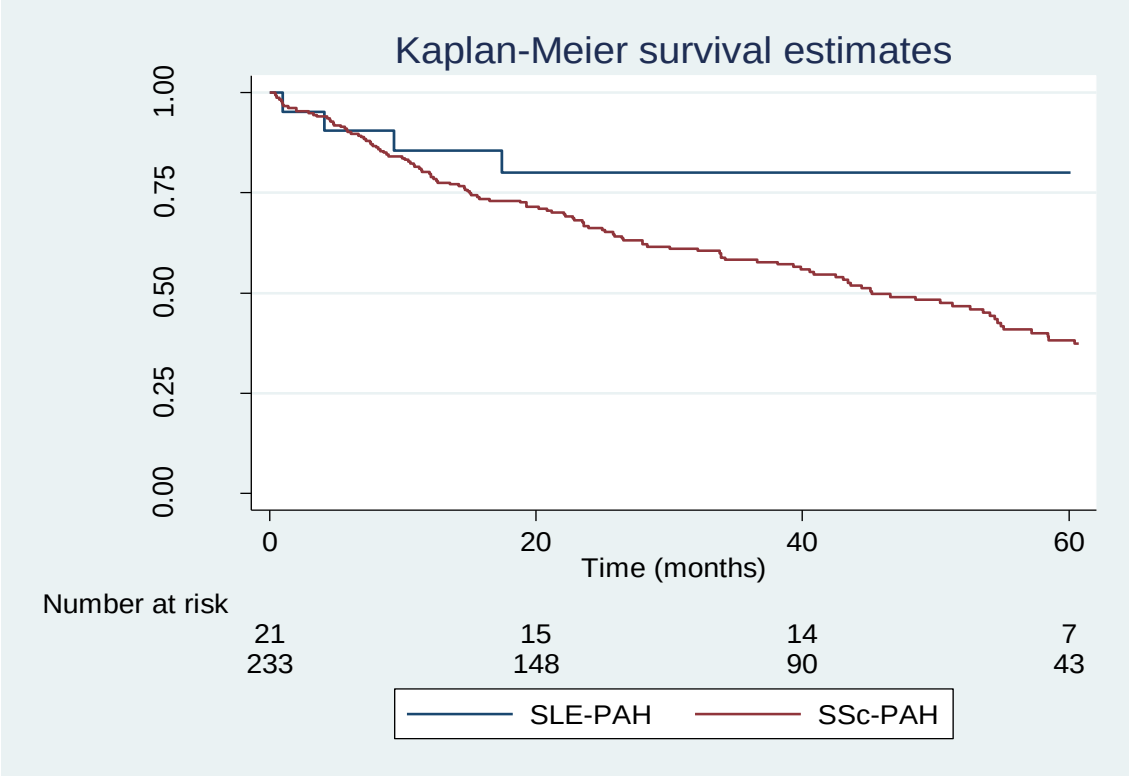
respectively, p=0.31). NT-pro-BNP values were also similar (SLE-PAH: n=9, mean 220 pmol/l. SSC-PAH: n=117, mean 248, p=0.84 for comparison).

Pulmonary function tests showed a lower FVC % predicted in SLE-PAH (n=8, mean 81.4%) compared to SSc-PAH (n=157, mean 94.7%, p=0.03 for comparison). Nonetheless DL_{CO} % predicted was lower in the SSc-PAH patients (SLE-PH: n=8, mean 52.7%. SSc-PH: n=139, mean 38.6%, p=0.0012 for comparison).

WHO Functional class was similar in the two groups (mean 3.0 in SLE-PAH vs 3.1 in SSc-PAH, p=0.93).

Six minute walking distance was on average 54 metres further in the SLE-PAH group (SLE-PAH: n=17, mean 301. SSc-PAH: n=178, mean 247, p=0.08 for comparison)

Figure 1. Kaplan-Meier survival in Patients with SSc-PAH and SLE-PAH



Survival in the two cohorts from the time of the diagnostic right heart catheter is shown in figure 1. Median survival was 45.2 months in SSc-PAH (95% CI 39-55). Median survival was

not reached in patients with SLE-PAH but 95% CI start at 76.8 months. Cox proportional hazards analysis shows that the diagnosis of SSc-PAH is associated with an odds ratio of 3.0 (95% CI 1.2,7.3, p=0.017) for mortality. On multivariable cox proportional hazards analysis, age (p<0.0005), functional class (p=0.003), gender (p=0.01) and baseline pulmonary vascular resistance (PVR, p<0.0005) are each independently associated with survival. There was a trend towards worse survival in patients with SSc-PAH even after adjustment for these factors (OR 2.3, CI 0.9,5.7. p=0.08).

However, median survival is better in SLE-PAH compared to SSC-PAH (log-rank test p=0.02). Median survival is 39.9 months in the SSc-PAH group (95% CI 30.9-45.2). Median survival was not reached in the SLE-PAH cohort, but the 95% confidence interval for the median survival starts at 76.8 months.

1 year survival is 81.4% (58-93) in SLE-PAH compared to 79.5% (74-84) in SSc-PAH. 5 year survival is 76% (95% CI 51-89) in the SLE-PAH cohort and 32.8% in the SSc-PAH cohort (95% CI 26-40).

	SLE-PAH (n=22)	**SSc-PAH (n=309)**
1 year	81.4% (58-93)	79.5% (74-84)
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Follow up catheterisation showed significantly more improvement in mPAP (-5.7 vs =0.6, p=0.01) and in PVR (-228 vs -38, p=0.006). A larger proportion showed any improvement in PVR in the SLE-PAH cohort (88% vs 62%, p=0.03).

Cox proportional hazards analysis shows that underlying diagnosis (SLE vs SSc) is not independently associated with survival after adjustment for age, baseline haemodynamics, and DL_{CO}.

In order to understand what else contributes to the difference in outcome in these two patient groups, we assessed the haemodynamics at follow up RHC. After initiation on pulmonary hypertension specific therapies with PDE5 inhibitors, ERAs or prostacyclins, RHC was repeated, usually at 3-6 months.

Repeat right heart catheterisation was performed in 17 of 21 patients with SLE-PAH and 166 of 234 patients with SSc-PAH. Despite similar baseline values, PVR was improved in 81% of patients with SLE-PAH compared to 55% of patients with SSc-PAH (p=0.045). The average PVR change was an improvement of 188 dynes.s.cm^{-5} in patients with SLE-PAH but an improvement of only 24 dynes.s.cm^{-5} in patients with SSc-PAH [Table 2].

Table 2. Change in Haemodynamics after PAH specific therapies

	SLE-PAH n=21	SSc-PAH n=234	p value
Change in PVR (dynes.s.cm^{-5})	-188 (n=16)	-24 (n=161)	0.028
Change in mPAP (mm Hg)	-4.6 (n=17)	+0.4 (n=166)	0.045
Any PVR improvement	81.3%	55.3%	0.045

Thus there is a clear difference in change in pulmonary vascular resistance in patients with SLE-PAH and SSc-PAH [Table 2]. However, the relative changes are small. The mean change is -5.5% in those with SLE-PAH (95% CI -46,35.0) and +3.3% in those with SSc-PAH (95% CI -4.1,10.8).

Cox proportional hazards analysis shows that absolute change in PVR is independently associated with mortality (OR 1.15 per 1 unit increase in PVR in wood units, 95% CI 1.08,1.23, p<0.0005), even after adjustment for age (OR 1.08 per year increase, 95% CI 1.05,1.11, p<0.0005), gender (2.21 for males, 95% CI 1.15,4.23, p=0.018), functional class (not significant, 0.87 so dropped) and baseline pulmonary vascular resistance (OR 1.22 per wood unit, 95% CI 1.16,1.29, p<0.0005).

Those patients with an improvement in PVR have a clearly better outcome than those who do not, with 42% less mortality (Odds ratio 0.58, 95% CI 0.36,0.92, p=0.02). Median survival in responders is 54.4 months (95% CI 33.9,71.6) and in non-responders it is 96.5 months (95% CI 53.6 -). Patients with any PVR response survive longer than those without a response (p=0.04 by log-rank).

Nonetheless, even after adjustment for age, gender, baseline PVR and change in PVR, patients with SSc-PAH tend to worse survival than those with SLE-PAH (odds ratio 4.2, 95% CI 0.98,18.4, p=0.054), suggesting that there may be other factors at play to explain the worse survival in SSc-PAH.

Table 3.

Variable	Odds ratio	CI	P
PVR better	0.58	0.36,0.92	0.02
Age	1.08	1.05,1.11	<0.0005
Gender	2.3	1.20,4.42	0.013
Functional Class	0.96	0.67,1.36	0.81

Discussion

We have shown that patients with SLE-PAH are different to patients with SSc-PAH. They are younger, less frequently male and tend to have slightly higher mean pulmonary artery pressures. Furthermore, patients with SLE-PAH show a more frequent and marked improvement in PVR after treatment with PH specific therapies. We have also shown that improvement in PVR at follow up right heart catheterisation is associated with better survival. Finally, we have shown that the difference in survival between the two cohorts is not entirely explained by these differences.

SLE-PAH may well be a different disease to SSc-PAH. Patients with SLE-PAH may have different pathophysiology, with more frequent pulmonary vasculitis and pulmonary thromboembolic disease in patients with SLE. The derangements in the immune system are different in patients with SLE and SSc, and this may impact on response to treatment.

Limitations of our study are its retrospective nature, leading to some incomplete data and limiting our ability to infer whether the improvements in PVR were due to treatment or to natural history of the disease.

Our data suggests that change in haemodynamics at 3-6 months is associated with survival, with about 42% less mortality in those who respond than in those who do not. This may have

implications for clinical practice as it demonstrates that even small improvements in PVR predict improved survival. Change in PVR may therefore be an important indicator that treatment is working and may be another useful surrogate measure of clinical improvement in clinical trials.

Conclusion

Compared to patients with SSc-PAH, patients with SLE-PAH are younger and have more preserved DLco. Initial pulmonary artery pressures are higher but haemodynamic responses to therapy in SLE-PAH are more common and of greater magnitude in SLE-PAH than in SSc-PAH. These differences may account for the markedly better survival in patients with SLE-PAH.

Chapter 6. Prevalence and significance of CT findings suggestive of pulmonary veno-occlusive disease in systemic sclerosis

B. E. Schreiber, G. Keir, D. Dobarro, C. Handler, S. Nihtyanova, J. Suntharaligam, N. Sverzelatti, G. Robinson, D. Hansell, A. U. Wells, C. P. Denton, J. G. Coghlan. Poster Abstract presentation, ACR, Washington, November 2012.

Abstract

Background

Recent reviews have suggested a high prevalence of pulmonary venoocclusive disease (PVOD) amongst patients with systemic sclerosis associated pulmonary hypertension. We tested this hypothesis on a large series of patients.

Methods

A retrospective study of 117 patients with systemic sclerosis who underwent CT of the chest within six months of a diagnostic right heart catheterisation. The CTs were blindly scored by two independent radiologists for extent of interstitial lung disease, vessel size and features of PVOD. Each lung quadrant was scored separately for interlobular septal thickening (IST) with score 0-5 and centrilobular nodules (CLN), score 0-3. Survival data was collected on all patients.

Results

Mean age was 57.8 (range 22-85). 78% were female. 84 patients had LcSSc, 32 had DcSSc and 1 had MCTD. CT scans were performed a mean of 2.7 months from the RHC.

There was limited or no ILD extent (<20%) in 46 patients (43%), indeterminate in 28% and extensive (>20%) in 30%. On right heart catheterisation 53% had precapillary PH while 47% did not.

Of 117 scans, 22 scans could not be fully reported by both radiologists. Of the remaining 95 patients, 49 had PAH and 46 did not. Of those with PH, 18 had <20% ILD, 18 had ~20% ILD and 13 had >20% ILD. There was a weak trend towards worse survival with more lung disease (HR 1.5, 95% CI 0.89,2.52, p=0.13).

Mean IST score was 1 (on a scale of 0-4) and mean CLN score was 0.63 (scale of 0-2). IST was not associated with extent of ILD (p=0.19 by chi-square), and nor was CLN (p=0.74, by chi-square).

IST did not correlate with PVR (R2=2%) whereas CLN did correlate with PVR (R2=15.7%).

On Cox proportional hazards analysis, PVR was a strong predictor of death (p=0.001). Increasing IST was associated with worse survival on univariate analysis (p=0.038), however this finding is lost (p=0.11) after adjusment for age.

Increasing CLN is strongly associated with higher mortality (p=0.013) even after adjustment for age, gender, extent of interstitial lung disease and mean pulmonary artery pressure (p=0.047). This is particularly so in patients without PH (p=0.004 on this multivariate analysis) rather than in patients with PH (where p=0.19 on multivariate analysis). However, not after adjustment for PVR (p=0.18).

Conclusion

Interlobular septal thickening and centrilobular nodules are frequently seen in patients with systemic sclerosis and are each associated with worse survival. However, IST increases with age and CLN increases with worsening pulmonary vascular resistance. We have not found that they are independent predictors of worse outcome in systemic sclerosis.

Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare variant of pulmonary hypertension characterised histologically by involvement of the pulmonary venule and clinically by a progressive course with poor response to pulmonary vasodilators, which may indeed precipitate pulmonary oedema. PVOD is associated with changes on computed tomography of the chest, especially lymphadenopathy, septal lines and centriloblar ground glass opacities.[54]

Small histopathological case series have suggested that pulmonary veno-occlusive disease may be more common in systemic sclerosis than in idiopathic pulmonary arterial hypertension.[55,56] In a recently reported French series, a high prevalence of these radiological findings were seen in patients with systemic sclerosis associated pulmonary hypertension, and these were associated with a high prevalence of pulmonary oedema following treatment with pulmonary vasodilators.[57]

However, whether these radiological features are present in patients with systemic sclerosis without pulmonary hypertension has not been fully explored. We sought to explore the clinical associations of interlobular septal thickening and centrilobular nodules in patients with systemic sclerosis with or without pulmonary hypertension and interstitial lung disease.

Patients and Methods

A retrospective study of 95 patients with systemic sclerosis who underwent CT of the chest within six months of a diagnostic right heart catheterisation. The CTs were blindly scored by two independent radiologists for extent of interstitial lung disease, vessel size and features of PVOD. Each lung quadrant was scored separately for interlobular septal thickening (IST) with score 0-5 and centrilobular nodules (CLN), score 0-3. Survival data was collected on all patients. Survival was collected from the NHS national database.

Analyses were performed using Stata 10.0. Scans were reported by two radiologists. For the purposes of these analyses, we determined that patients who were scored by both radiologists as

having extensive disease as extensive, those scored by both radiologists as limited and the rest as intermediate.

Results

Mean age was 59.2 (range 22-85). 80% were female. 69 patients (73%) had limited scleroderma while 26 (27%) had diffuse disease. CT scans were performed a mean of 2.6 months from the RHC (range 0-6 months).

Parenchymal disease (>5%) was present in half of the patients (48 patients, 50.5%). Parenchymal disease was seen in similar proportions in limited (37 of 69 patients) and diffuse (11 of 26 patients) scleroderma (chi squared =0.33).

In those with parenchymal lung disease the overall disease extent was scored as limited (<20%), indeterminate or extensive (>20%). The proportions were reported by each radiologist (kappa 0.67). 42-61% had limited lung involvement, 5-6% had indeterminate and 29-46% had extensive lung involvement. Overall, 41 patients (43%) had no or <20% lung involvement, 29% had intermediate lung involvement and 25% had extensive lung involvement. This did not differ by disease subtype (χ^2 p=0.25).

All patients also underwent right heart catheterisaton. Mean pulmonary artery pressure was 28.2 mmHg with no difference between those with interstitial lung disease (mean pressure 27.4 mmHg) and those without (mean pressure 28.9 mmHg, p=0.52).

	Mild ILD 0-20% (n=41)	Moderate ILD Approx 20% (n=29)	Severe ILD More than 20% (n=25)
Age (years)	59.9	60.9	56.2
Female (%)	78.0	82.8	80.0
Limited subtype (%)	78.0	75.9	60.0
Mean PA (mmHg)	26.5	33.2	25.1
Wedge pres (mmHg)	11.1	10.8	8.3
Precapillary PH	43.9%	65.5%	48%
PVR (dynes.s.cm^{-5})	288	454	324
5 year survival	72% (54-83)	71% (49-84)	44% (22-64)

Table 1. Demographics, disease subtype, pulmonary haemodynamics and survival by ILD group

Survival did not differ significantly among these groups.

Interlobular septal thickening (IST)

IST scores are shown in **Figure 1a**. Agreement between radiologists was low (kappa 0.17-0.45).

IST was strongly associated with age, but it was not associated with presence of PH or ILD (**Table 2, Figure 1b**). Mortality was higher in patients with IST (HR 2.12, 95% CI 1.12-4.01, p=0.02) but not after adjustment for age.

	No interlobular septal thickening **n=60**	Interlobular septal thickening **n=35**	P value
Age	55.9	64.9	0.0004
Gender	85% female	71% female	0.11
Presence of ILD	53%	46%	0.48
Presence of PH	51.7%	51.4%	0.98
PCWP	10.2 mmHg	10.4 mmHg	0.88

Table 2. Patient characteristics by presence of interlobular septal thickening

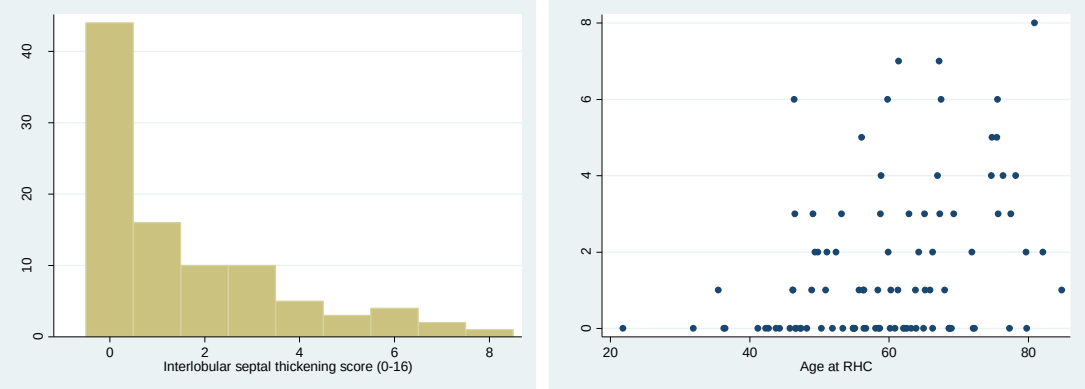


Figure 1a and 1b. Distribution of interlobular septal thickening scores. Distribution of interlobular septal thickening score by age.

Centrilobular nodules (CLN)

CLN scores are shown in **Figure 2a**. Only 12% had CLN. Agreement between radiologists was poor (Kappa 0.16-0.49).

CLN was not associated with age or presence of ILD (**Table 3**). However, it was associated with PH and correlated with PVR (R^2=15.7%, **Figure 2b**).

Significant CLN is strongly associated with higher mortality (HR 3.19, 95% CI 1.34-7.64, p=0.009). This persists after adjustment for gender and extent of interstitial lung disease but not after adjustment for PVR.

Of 22 patients with significant CLN or IST, 17 had PH and were treated with PDE5 (n=11), ERA (n=12), prostacyclins (n=7). None clinically had PVOD.

	No CLN **n=83**	CLN **n=12**	P value
Age	58.8	62.1	0.39
Gender	79.5% female	83.3% female	0.76
Presence of ILD	47%	75%	0.07
Presence of PH	47%	83%	0.02
PCWP	10.3	10.5	0.85

Table 3. Patient characteristics by presence of centrilobular nodules.

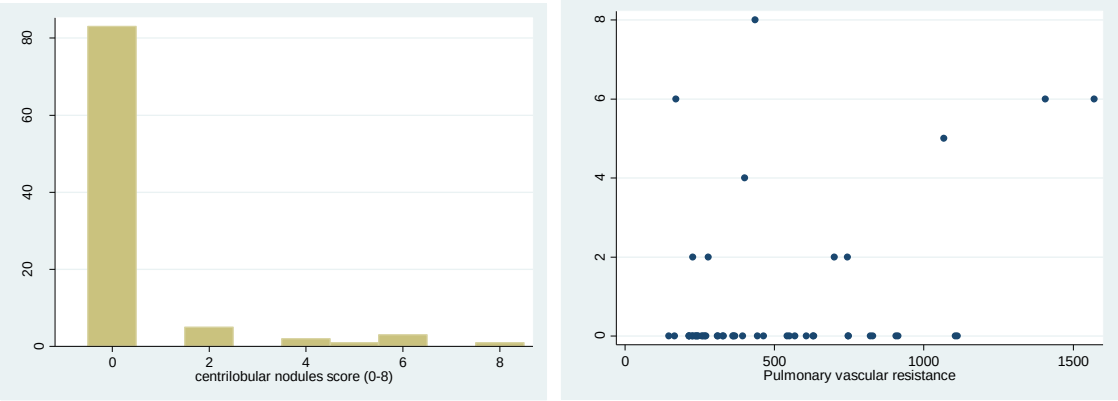


Figure 2a and 2b. Distribution of scores for centrilobular nodules and relationship between pulmonary vascular resistance and centrilobular nodule score.

Discussion

In this study we have shown that interlobular septal thickening and centrilobular nodules are common findings present in 37% and 12% of scans respectively. Agreement between two blinded independent radiologists was poor.

We found that interlobular septal thickening was associated with older age. We confirmed that IST is a negative prognostic factor but found that increasing age was an important confounder. Case notes review of the patients with significant IST and CLN found that although patients were treated with PDE_5 inhibitors, ERA and prostacyclins, of 17 patients with PH and significant IST or CLN, none had PVOD clinically.

There are several lines of evidence pointing to increased risk of pulmonary veno-occlusive disease in scleroderma. A Dutch study compared histology from lung tissue of 8 patients with scleroderma associated pulmonary arterial hypertension and 11 idiopathic pulmonary arterial hypertension patients. They found focal fibrosis of veins or venules and associated capillary congestion in 4 of the 8 scleroderma patients and in 3 of 11 patients with idiopathic PAH. Of the 8 patients, they describe CT findings 'associated with PVOD' in 7, including ground glass in 6 of 8 patients and septal lines in 3 of 8 patients.[55]

In another histopathological study, Dorfmuller and colleagues compared lung samples from 8 patients with connective tissue disease associated pulmonary arterial hypertension (5 postmortem, 3 after lung transplantation) with 29 patients with pulmonary arterial hypertension due to other causes. They found significant obstructive pulmonary vascular lesions predominating in veins/preseptal venules in 6 (75%) of 8 patients with CTD associated pulmonary arterial hypertension but in only 5 (17.2%) of 29 non–connective tissue patients with pulmonary arterial hypertension.[56]

In an important early French study of patients with pulmonary arterial hypertension who had undergone lung biopsies between 1991 and 2004, 24 patients with pulmonary veno-occlusive disease were compared to 24 patients with plexiform lesions but no veno-occlusive disease. These patients had pulmonary arterial hypertension which was idiopathic, familial, or associated with a history of anorexigen use. The CTs of 20 patients with biopsy-confirmed pulmonary veno-occlusive disease were compared to 13 patients with PAH by two blinded experienced radiologists. Septal lines and centrilobular ground glass opacities were more common in patients

with PVOD than with controls. Of the 24 patients, 16 were treated with specific therapies, and 8 episodes of pulmonary oedema occurred in 7 patients. Patients with connective tissue diseases were excluded from this study.[54]

A recent French series found a high prevalence of centrilobular ground-glass opacities in SSc-PAH compared to SSc without PH (46.2% versus 10.7%), and of septal lines (88.5% versus 7.1%).[57] They found a correlation between these signs and pulmonary oedema after initiation of PH specific therapies.

A recent review of the CT findings in PVOD highlights the non-specific nature of some of these features.[58] We found that these CT signs were common in scleroderma patients and were adverse prognostic features. However, our analysis suggests that IST and CLN may reflect increasing age and worse PH respectively. Interlobular septal thickening and centrilobular nodules are not specific findings. They are common in scleroderma patients without pulmonary hypertension. They are indeed markers for poor prognosis but they may be reflecting the presence of known risk factors, namely older age and worse pulmonary hypertension respectively. In our patients they did not correlate with clinical features of pulmonary veno-occlusive disease.

Appendix: Proforma for CT chests

Main pulmonary artery & Pericardium

Main PA short axis diameter and adjacent ascending aorta (at the level of the PA bifurcation) 0= aorta > main PA, 1= main PA=aorta , 2= main PA > aorta	
Main PA short axis diameter (where the main PA is in continuity with the right main PA)	
Anterior superior pericardial recess 0= no fluid or thickening, 1= minimal thickening/fluid (<10mm), 2= extensive thickening /fluid (>10mm)	

Lobar characteristics

Right upper lobe RUL apical segmental artery short axis diameter		**Left upper lobe** LUL apical segmental artery short axis diameter	

Artery:bronchus ratio (score 1-5)		Artery:bronchus ratio (score 1-5)	
Interlobular septal thickening (score 1-5) - central, peripheral or mixed		Interlobular septal thickening (score 1-5) - central, peripheral or mixed	
Centrilobular nodules 0= not visible, 1=visible, 2=profuse		Centrilobular nodules 0= not visible, 1=visible, 2=profuse	
Mosaicism 0= 0%, 1=1-25%, 2= 26-50% 3= 51-75%, 4= 76-100%		Mosaicism 0= 0%, 1=1-25%, 2= 26-50% 3= 51-75%, 4= 76-100%	
Predominant pattern Ground glass Reticular Mixed		Predominant pattern Ground glass Reticular Mixed	
Right Lower lobe RLL apical segmental artery short axis diameter		**Left Lower Lobe** LLL apical segmental artery short axis diameter	
Artery:bronchus ratio (score 1-5)		Artery:bronchus ratio (score 1-5)	
Interlobular septal thickening (score 1-5) - central, peripheral or mixed		Interlobular septal thickening (score 1-5) - central, peripheral or mixed	
Centrilobular nodules 0= not visible, 1=visible, 2=profuse		Centrilobular nodules 0= not visible, 1=visible, 2=profuse	
Mosaicism 0= 0%, 1=1-25%,2= 26-50% 3= 51-75%,4= 76-100%		Mosaicism 0= 0%, 1=1-25%,2= 26-50% 3= 51-75%,4= 76-100%	
Predominant pattern Ground glass Reticular Mixed		Predominant pattern Ground glass Reticular Mixed	
Overall Disease Extent Limited Extensive Indeterminate (<20%) (>20%)			

Detailed scoring instructions

Window level : Settings of 1500 width and a level of -500 HU
(main PA, right and left main PA were assessed on mediastinal window settings of width 400, and level of 40 HU)

Main PA and adjacent ascending aorta
Comparative sizes of the short axis diameter of the main PA and adjacent ascending AA on axial CT at the level of the bifurcation of the main PA, where the left and right main PAs are judged to be present in equal measure
0= aorta larger than main PA
1= main PA equal in size to aorta
2= main PA definitely larger than the aorta

Main PA short axis diameter
Main PA short axis diameter was obtained on axial CT section where the main PA is in contiuity with the right main PA (in the cases where more than one CT section fulfilled the criteria, the largest short axis diameter was recorded. The reading was taken at a point equivalent to within 1 cm of the mid AP diameter of the adjacent ascending aorta

Pericardium
Abnormalities of the anterior superior pericardial recess between the ascending aorta and pulmonary trunk
0= no fluid or thickening
1= minimal thickening of, or fluid within, the anterior-superior pericardial recess (depth <10mm)
2= extensive thickening of, or fluid within, the anterior pericardial recess (depth >10mm

Artery:bronchus ratio
ABR is visually estimated for the upper and lower lobe segmental pulmonary arteries and their accompanying bronchus.
1= ratio of short axis diameter of artery to short axis outer diameter of bronchus less than 0.75
2= ratio between 0.75 and ≤1.25
3= ratio between 1.25 and <2
4= ratio between 2 and ≤ 3
5= ratio >3

Interlobular septal thickening
0= no visible interlobular septa
1= <5 visible interlobular septa
2= ≥5 visible interlobular septa over <50% of the pleural surface
3= interlobular septa of >50% of the pleural surface
4= profuse interlobular septa

Mosaicism
Extent of decreased attenuation attributable to vascular disease
0= 0%
1= 1-25%
2= 26-50%
3= 51-75%
4= 76-100%

Overall disease extent
The extent of reticular change and ground glass change was evaluated from the origin of the great vessels to immediately above the right hemidiaphragm and scored as:
Limited involvement: <20%
Extensive involvement: >20%
Indeterminate

Chapter 7. The Double Whammy: Survival in Systemic Sclerosis with Interstitial Lung Disease and Pulmonary Hypertension

Schreiber BE et al, Oral Presentation at American Congress of Rheumatology Annual Meeting, Chicago 2011

Abstract

Background

Predictors of survival in systemic sclerosis patients with concurrent interstitial lung disease and pulmonary hypertension are poorly understood.

Methods

Retrospective analysis of a large regional single centre cohort of patients with systemic sclerosis associated pulmonary hypertension. Inclusion criteria were a diagnosis of systemic sclerosis, precapillary pulmonary hypertension as defined by mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and FVC < 70% predicted and presence of significant lung fibrosis on CT.

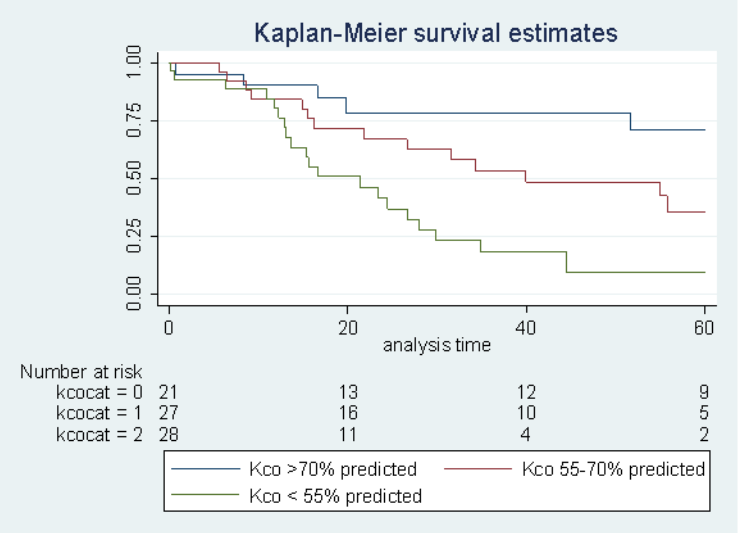
Results

76 patients were identified. Mean age was 54.9 years. 51 (67%) female. 34 (44.7%) were classified to diffuse subset. Mean haemodynamics were: mPAP 37.3, PVR 554.6 dynes.s.cm-5. Median survival was 34.3 months (95% CI 23.4-55.7).

The following variables did not predict survival on univariable analysis: age (p=0.09), gender (p=0.59), right atrial pressure (0.47). heart rate (0.36), cardiac output (0.29), cardiac index (0.76), mean pulmonary artery pressure (p=1.00), pulmonary vascular resistance (p=0.08), oxygen saturation (p=0.41), mixed venous saturation (p=0.23), systolic blood pressure (p=0.37), diastolic blood pressure (p=0.10), six minute walking distance (p=0.10, n=47), NTproBNP (p=0.98, n=27), FVC % predicted (p=0.72), anti-centromere antibody status (p=0.31), anti-topoisomerase-1 antibody status (p=0.12).

Significant variables on univariate analysis were functional class (p=0.007), Dlco % predicted (p=0.03), FVC/DLCO (p=0.006) and Kco % predicted (p<0.0005, n=76). On multiple variable Cox analysis with these four variables, Kco % predicted is the only significant predictor (p=0.017).

Kco % predicted has tertiles at 54.2 and 69.6. Kco % predicted was grouped into tertiles: <55%, 55-70%, >70%. The hazard ratio associated with dropping by one category is 2.4 (95% CI 1.5-3.7).



The survival differs in the three groups (p=0.0002 by log-rank). 1, 3 and 5 year survival by group is given below:

	1 yr survival	3 yr survival	5 yr survival
Kco > 70% predicted	90.3% (67-98)	78.9% (53-92)	71.0% (43-87)
Kco 55-70% predicted	84.4% (63-94)	53.4% (32-71)	36.0% (16-57)
Kco < 55% predicted	80.4% (59-91)	18.5% (6-37)	9.2% (2-25)

Conclusions

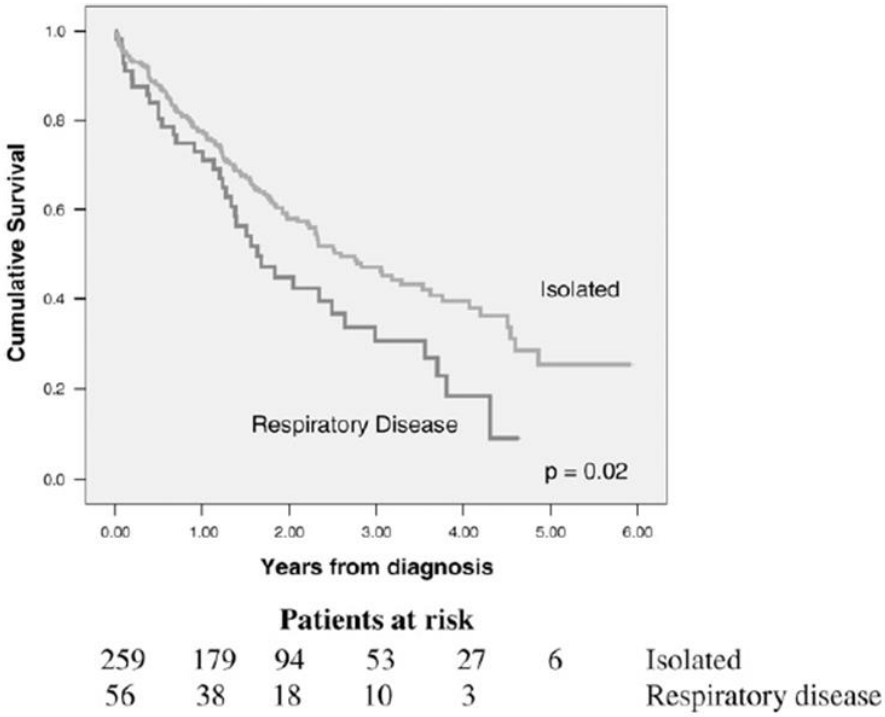
Patients with systemic sclerosis, interstitial lung disease and pulmonary hypertension have a poor survival. We found that no demographic and haemodynamic variables predicted survival in this patient cohort.

On multiple variable models the only significant independent predictor of survival was Kco % predicted, which is the calculated diffusion of carbon monoxide adjusted for alveolar volume. KCO may reflect the extent of impairment of parenchymal dysfunction by combining both interstitial and vascular components of the disease process.

Introduction

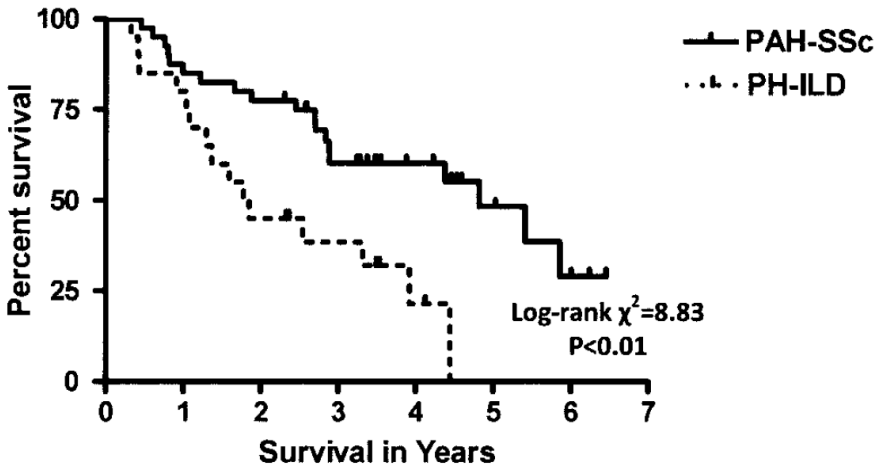
Patients with systemic sclerosis often have both interstitial lung disease (30-40% lifetime risk) and pulmonary hypertension (10-15% lifetime risk). The concept of "disproportionate PH" remains controversial. Prognostic factors are not well understood in this cohort.

Previous work from the UK National Audit has compared 259 patients with SSc-PAH to 56 patients with SSc-ILD-PH. Survival was worse with respiratory disease (p=0.02).[53]



Source: Reference 53.

A study from John Hopkins hospital in Baltimore compared 39 patients with SSc-PAH to 20 patients with SSc-ILD-PH. They found worse survival in patients with lung disease. Survival was 87% at 1 year , 79% at 2 years and 64 % at 3 years in SSc-PAH. By comparison it was 82% at 1 year, 46% at 2 years and 39% at 3 years in SSc-ILD-PH.[59]



Source: Reference 59.

Table 4. Risk factors for mortality or transplant in patients with ILD-associated PH and patients with PAH*

	HR (95% CI)	*P*
ILD-associated PH		
African American race	2.76 (0.92–8.3)	0.07
DLco, % predicted	0.93 (0.87–0.98)	0.02
Mean pulmonary artery pressure, mm Hg	1.07 (0.99–1.15)	0.09
PVR index, Wood units/m^2	1.06 (1.00–1.19)	0.04
PAH		
Cardiac index, liters/minute/m^2	0.41 (0.19–0.97)	0.04
PVR index, Wood units/m^2	1.05 (1.02–1.09)	0.02

Source: Reference 59.

In this study we compared survival of patients with SSc, pulmonary hypertension and interstitial lung disease (SSc-PH-ILD) as defined by pulmonary function tests (PFTs) to those with preserved lung volumes (PAH). We analysed the variables associated with outcome in patients with SSc and PH-ILD.

Patients and Methods

Patients

We analysed a prospectively collected database of all diagnostic right heart catheter (RHC) studies performed on SSc patients in a national PH referral centre from 1995-2010. Inclusion criteria were a diagnosis of SSc (including SSc overlap syndromes) and precapillary PH (mean

pulmonary artery pressure (mPAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg). Patients for whom contemporary PFTs (FVC % predicted, DL_{CO} % predicted and K_{CO} % predicted within six months of the RHC) were not available were excluded from the analysis.

Of 844 patients who underwent RHC, 78 patients had postcapillary PH and 437 had precapillary PH. Of these 437 patients, complete PFTs were available in 227 patients who formed the study group. An FVC threshold of below 70% predicted was taken as significant lung disease. Of these 227 patients, 76 had FVC < 70% predicted (SSc-PH-ILD) and 151 had FVC ≥ 70 % predicted (SSc-PAH). These two patient groups were compared, and the association between baseline data and survival in patients with SSc-PH-ILD were assessed.

Investigations were performed as part of routine clinical care. Catheterization was performed in scleroderma patients with clinical suspicion of PH. In general, RHC was considered in any patient with tricuspid jet velocity >3.2 metres/second, in patients with tricuspid jet velocity between 2.8 and 3.2 m/s if there was any clinical suspicion of PH and in patients with tricuspid jet velocity below 2.8 m/s if there was a strong clinical suspicion or unexplained progression of exertional dyspnea.

Clinical Data

Oxygen saturation measurements were taken at the time of the RHC. This was measured on room air at the finger if there was an excellent signal or by femoral arterial puncture and blood gas analysis. Patients taking supplementary oxygen had their oxygen stopped to establish baseline oxygen saturation. One patient could not be taken off supplementary oxygen and was excluded from the analysis.

PFTs were performed at the Royal Free Hospital or the Royal Brompton Hospital.

Data Analysis

Analyses were performed using STATA® software (STATA version 10.0 for Windows, Texas, USA). Data were expressed as means (SD) or medians (range), depending on distribution. Group

comparisons were made using Student's *t* test or chi-square test as appropriate. A *P* value of less than 0.05 was considered significant.

For survival analysis, univariate analyses were performed using Kaplan-Meier curves and log-rank test for categorical variables and univariate Cox proportional hazard regression for continuous variables.

Variables with p value under 0.2 were carried forward as potential variables for inclusion in the final model. Age and gender were also included. The least significant variables were then removed sequentially until only variables with strong statistical associations ($p<0.05$) were included.

Results

Study Population

Within the study sample of 227 patients, patients were classified as PAH if FVC $\geq$ 70% predicted (n=151, mean FVC 94.2% predicted) and SSc-PH-ILD if FVC < 70% predicted (n=76, mean FVC 54.2 % predicted). The mean number of days between PFTs and RHC was 51.3 (SD 51.1). Compared to the patients in the PAH group, patients in the SSc-PH-ILD group were younger, more frequently male and more commonly had diffuse subset scleroderma and anti-scleroderma 70 antibodies. The SSc-PH-ILD patients were more frequently in worse functional class. Haemodynamic measurements at RHC were similar in the two groups.

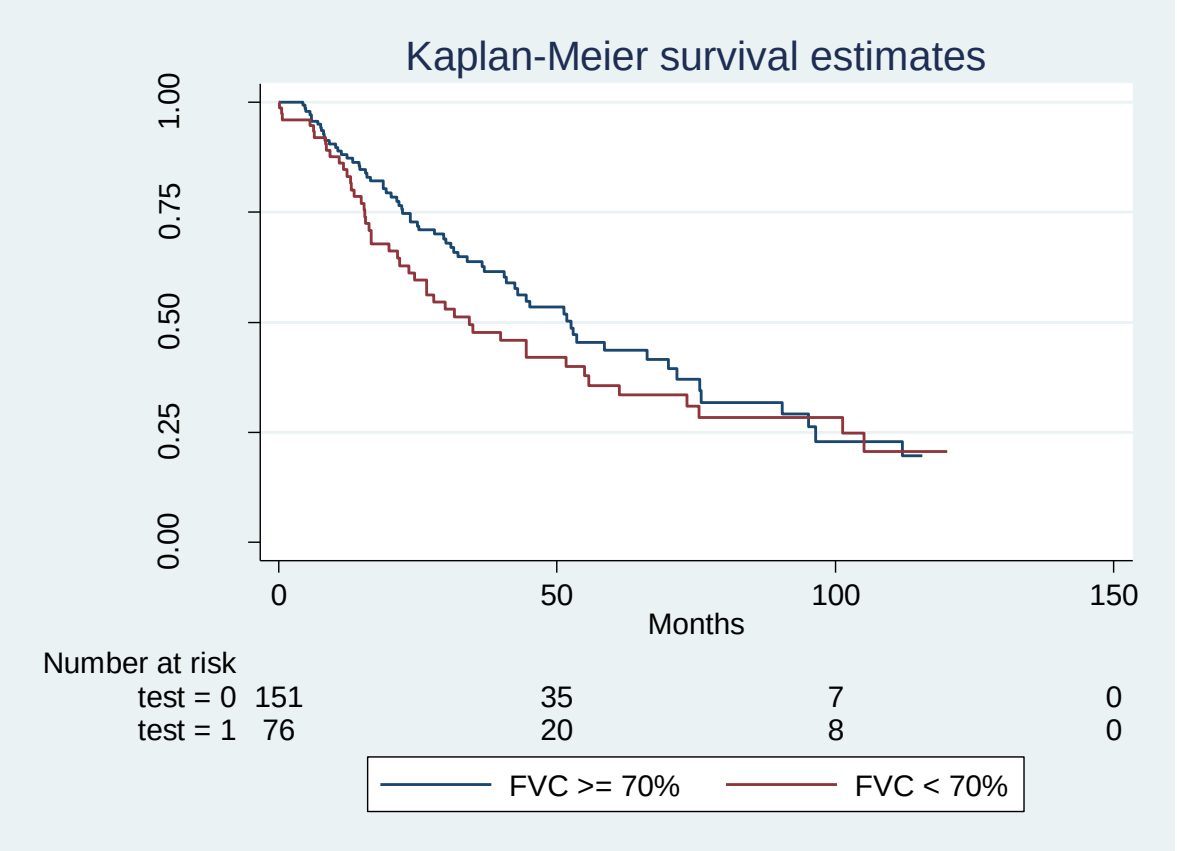
	SSc-PAH (FVC ≥ 70% n=151)	SSc-PH-ILD (FVC < 70% n=76)	p value
Age	61.2	54.9	0.0001
Gender	18.5% male	32.9% male	0.016*
Ever smoker	55/103	22/53	0.14*
LcSSc subset	128/147, 87.1%	39/73, 53.4%	<0.0005*
DcSSc subset	19/147, 12.9%	34/73, 46.6%	<0.0005*
Anti-Centromere	53.4% (n=131)	14.0% (n=57)	<0.0005*
Anti-Scl70	6.6% (n=121)	35.6% (n=59)	<0.0005*
Oxygen saturation	94.4% (n=146)	93.4% (n=74)	0.45*
DLco % predicted	40.9 %	31.1 %	<0.0005
Kco % predicted	53.0 %	61.5 %	0.0003
Heart rate	82	84	0.29
Mean RA pressure	7.4	7.7	0.65
Mean PA pressure	38.7	37.3	0.36
Mean wedge pressure	9.6	9.3	0.48
PVR (dynes.s.cm^{-5})	572.4	554.6	0.73
Functional class	2.9 (n=142)	3.3 (n=73)	<0.0005*
Six minute walk	248 m (n=101)	220 m (n=37)	0.23
NTproBNP	190 pmol/l (n=66)	136 pmol/l (n=17)	0.44

* χ^2 square test

Comparison of Survival

Median survival across both groups was 45.1 months (95% CI for mean 36.6-58.5). Median survival was 52.6 (95% CI 40.8-71.6) in Group 1 and 34.3 (23.4-55.7) in Group 3. After adjustment for age and gender, the diagnostic group was not significantly associated with

outcome (HR 1.30, p=0.20, CI 0.87-1.96). 1,2 and 3 year survival were 88%, 73% and 64% in PAH patients compared to 85%, 61% and 48% in SSc-PH-ILD patients. Overall survival in the first three years was better in the PAH patient group (p=0.03 by log-rank), but the difference was not significant over the first 5 years as a whole (p=0.10 by log rank) or over the first ten years (p=0.20 by log rank).



Survival in SSc-PH-ILD: Univariate Model

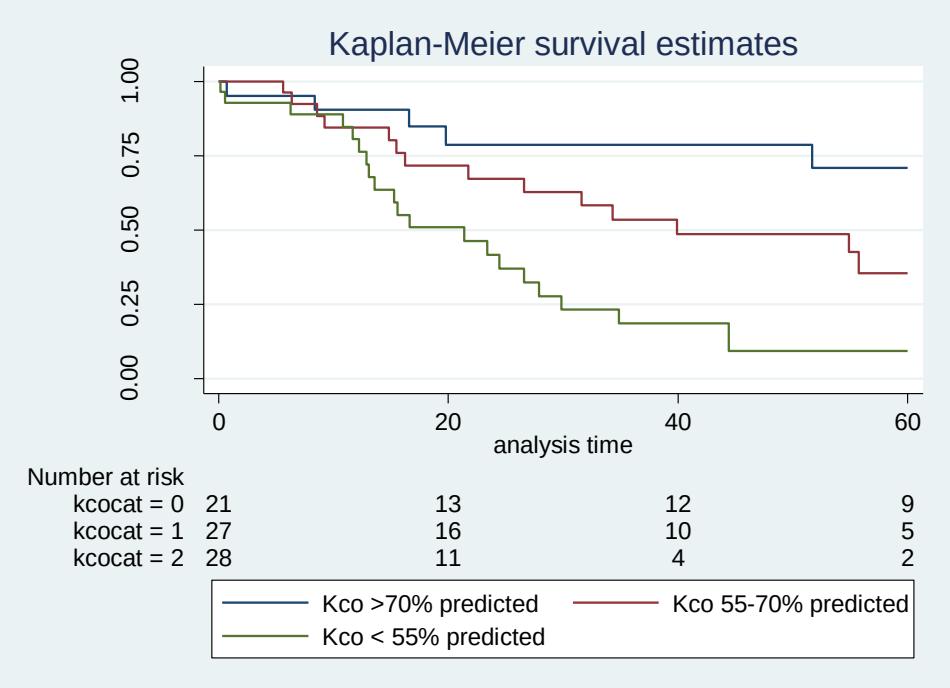
We studied the 76 patients with SSc-PH-ILD. As detailed above, mean age in this group was 54.9 years. 51 (67%) were female. 34 (44.7%) were classified as diffuse cutaneous systemic sclerosis subset. The mean pulmonary haemodynamics on right heart catheterisation were: mPAP 37.3 mmHg, PVR 554.6 dynes.s.cm^{-5}. The median survival in this group was 34.3 months (95% CI 23.4-55.7).

The following variables did not predict survival on univariable analysis: age (p=0.09), gender (p=0.59), right atrial pressure (0.47). heart rate (0.36), cardiac output (0.29), cardiac index

(0.76), mean pulmonary artery pressure (p=1.00), pulmonary vascular resistance (p=0.08), oxygen saturation (p=0.41), mixed venous saturation (p=0.23), systolic blood pressure (p=0.37), diastolic blood pressure (p=0.10), six minute walking distance (p=0.10, n=47), NTproBNP (p=0.98, n=27), FVC % predicted (p=0.72), anti-centromere antibody status (p=0.31), anti-topoisomerase-1 antibody status (p=0.12).

Significant variables on univariate analysis were functional class (p=0.007), Dlco % predicted (p=0.03), FVC/DLCO (p=0.006) and Kco % predicted (p<0.0005, n=76). On multiple variable Cox analysis with these four variables, Kco % predicted is the only significant indicator (p=0.017).

Kco % predicted has tertiles at 54.2 and 69.6. Kco % predicted was grouped into tertiles: <55%, 55-70%, >70%. The hazard ratio associated with dropping by one category is 2.4 (95% CI 1.5-3.7).



The survival differs in three groups (p=0.0002 by log-rank). 1, 3 and 5 year survival by group is given below:

	1 yr survival	3 yr survival	5 yr survival
Kco > 70% predicted	90.3% (67-98)	78.9% (53-92)	71.0% (43-87)
Kco 55-70% predicted	84.4% (63-94)	53.4% (32-71)	36.0% (16-57)
Kco < 55% predicted	80.4% (59-91)	18.5% (6-37)	9.2% (2-25)

Discussion

We have shown that SSc patients with PH-ILD have different demographics to patients with SSc-PAH: They are younger and more frequently male. In addition, they more commonly have diffuse scleroderma with anti-scleroderma 70 antibodies. The DLco is lower and the Kco is higher in the PH-ILD patients. Haemodynamic measurements at RHC are similar in the two groups, but patients with PH-ILD tend to have worse functional class.

The variables most closely associated with mortality in patients with SSc, ILD and PH is a low Kco % predicted. We found that Kco % predicted is more closely associated with survival than DLco % predicted or FVC % predicted / DLco % predicted. Kco % predicted is calculated on a single maneouver in which a gas mixture containing small amounts of carbon monoxide and helium is inhaled. The concentration of these two gases in the exhaled air allows estimation of diffusion of carbon monoxide and alveolar volume respectively. This may be more accurate than separate measurements of FVC % predicted and DLco % predicted for two reasons: Firstly, because the tests are done simultaneously and secondly because there is no forced maneuver and the Kco % predicted test is therefore less effort dependent. We found that despite lower DLco % predicted in the PH-ILD patients the Kco % predicted is higher on average. This has not been observed previously to our knowledge. It may be because the efficiency of the lung in interstitial lung disease is not directly proportional to the change in alveolar volume. A lower Kco % predicted reflects dysfunction in gas diffusion which is disproportional to the volume reduction, which may be a measure of pulmonary vascular insufficiency.

A recently published analysis by French investigators of 97 patients with SSc and PH, 47 of whom had ILD, found similar demographic differences between the two groups. They found a

trend towards worse survival in patients with PH-ILD over the first three years (3-year survival of 47% vs 71%, respectively, p=0.07). The poor prognostic factors in their analysis were pericardial effusion and lower DLco. Kco was not included in their analysis.[60]

American investigators described a cohort of 59 patients, of whom 20 had SSc-ILD-PH. They found worse survival in the SSc-PH-ILD group than the SSc-PAH group with 3-year survival rates of 39% and 64% respectively ($p<0.01$ by log-rank). Poor prognostic factors (for mortality or transplant) in the 20 patients with ILD-PH were DLco % predicted and PVR. Kco % predicted was not included in their analysis.[59]

Our finding of 3 year survival rates of 64% in SSc-PAH and 48% in SSc-PH-ILD are very similar to the French and American reports. Intriguingly, although we found a significant difference in survival over the first three years (p=0.03 by log-rank) there was convergence later on, so that survival over 5 years is no longer significantly different (p=0.10), although the numbers of patients are smaller so this is difficult to interpret.

It is not known whether PAH specific therapies are effective in patients with ILD-PH. In a French series from two centres of 70 patients with SSc and ILD-PH who were treated with PAH specific therapies survival was dismal with only 21% surviving 3 years.[61]

Our study has several limitations. We classified patients on the basis of PFTs rather than computed tomography scanning. Although we were constrained by availability of CT data. PFTs have strengths in that they are widely available, safe and are routinely performed in patients with SSc. In addition, studies based on CT require scoring which is not widely available outside academic studies. In addition, the threshold of FVC 70% was suggested by an analysis which combined CT scans with PFTs in a SSc cohort.[62] We did not have six minute walking data and NTproBNP on most patients and could not robustly analyse these variables. We did not include treatment in the analysis, although most patients with SScPH-ILD are not treated with PH specific therapies.

We have shown that patients with SScPH-ILD have worse survival in the first three years compared to PAH, despite similar haemodynamics at RHC. Important prognostic factors are functional class and Kco % predicted. Mean pulmonary artery pressures and pulmonary vascular resistance are not associated with survival and should not form the basis for management decisions. Further studies are needed to clarify which treatments are effective in this context.

Chapter 8. A model to predict survival in patients with systemic sclerosis associated pulmonary hypertension

***Schreiber BE**, Keir G, Valerio C, Handler C, Wells AU, Denton CP, Coghlan AU. Systemic Sclerosis associated Pulmonary Arterial Hypertension. A score to predict mortality. Oral presentation. Abstract 19327, American Thoracic Society, Denver, May 2011*

Objective

The leading causes of mortality in systemic sclerosis (SSc) are interstitial lung disease (ILD) and pulmonary hypertension (PH).[63] ILD occurs in about 30% of patients and PH in 10-15% of patients.**Error! Bookmark not defined.** It is known that interstitial lung disease and worsening pulmonary vascular resistance are associated with poor outcome in SSc-PH.[59] We sought to develop a prognostic score for patients with SSc-PH to combine haemodynamic and lung function data.

Patients and Methods

Patients

Consecutive patients (n=838) with SSc were referred to the Royal Free Pulmonary Hypertension service (London, UK) and had their first RHC between September 1996 and May 2010. Investigations were performed as part of routine clinical care. Of these patients 417 were found to have pulmonary arterial hypertension at right heart catheter (defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and pulmonary capillary wedge pressure

(PCWP) < 15 mmHg). Of these patients, DL_{CO}% predicted was unavailable in 186, FVC % predicted was unavailable in 179 and SpO_2 was unavailable in 21. In all, 202 patients were excluded because of incomplete pulmonary function test data. We studied the 215 patients with SSc-PAH who had SpO_2, FVC % predicted and DL_{CO} % predicted within six months of the RHC.

Clinical Data

Pulse oximetry measurements were taken at the time of the RHC. Data on autoantibodies, weight and height were also collected. Patients with SSc overlap syndromes were included. Patients were classified as limited cutaneous or diffuse cutaneous subtype according to the criteria described by LeRoy et al.**Error! Bookmark not defined.** Our criteria for cardiac catheterization have been previously reported.[26]

Data Analysis

Analyses were performed using STATA® software (STATA version 10.0 for Windows, Texas, USA). Data were expressed as means (SD) or medians (range), depending on distribution. Group comparisons were made using Student's *t* test. Survival analyses were compared using Log-Rank. A *P* value of less than 0.05 was considered significant.

Results

Patient Characteristics

We compared the patients in the study sample to those excluded [Table 1]. Our 215 patients were followed for an average of 24.5 months (range 0-147), a total of 616 patient-years.

Table 1 Descriptive statistics for patients

Characteristic	Mean (SD) or % study sample n=215	Mean (SD) or % excluded n=202	P value
Age (years)	59.0 (11.3)	60.5 (12.4)	0.18
Males	23.7 %	13.4 %	0.01
mPAP (mmHg)	38.1 (11.0)	40.1 (12.8)	0.08
SpO_2%	94.1 (4.0) %	93.6 (4.7) (n=181)	0.20

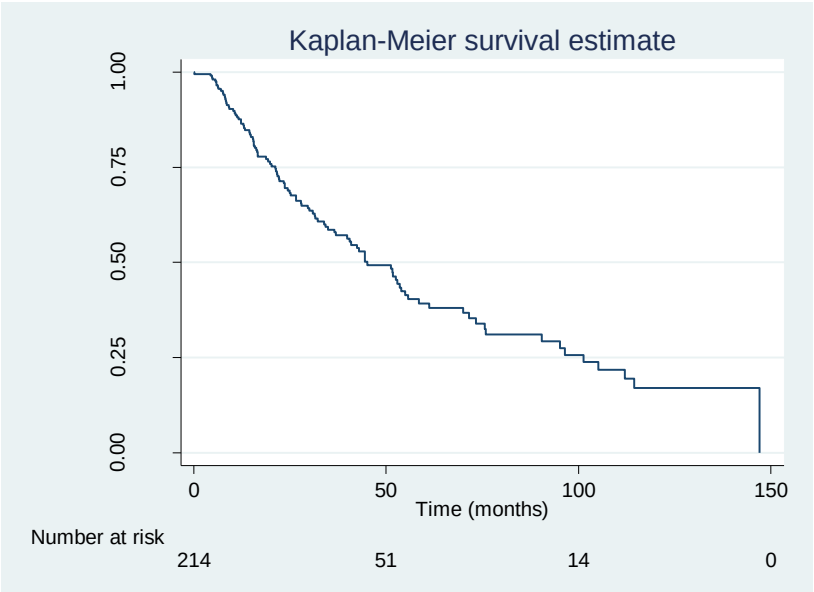
Further baseline characteristics of the study cohort are given in table 2.

Table 2 Study participant characteristics

Variable	Mean values (range)
FVC % pred	81.3 (27.4-139.6)
DL_{CO} % pred	37.2 (6.8-82.1)
SpO2% pred	94.1 (71-100)
Clinically LcSSc	76.6% (n=209)
Clinically DcSSc	23.4% (n=209)
ANA	95.2% (n=189)
Anti-centromere +ve	42.5% (n=179)
Anti-Scl70 +ve	16.4% (n=171)

Overall Survival of Patients

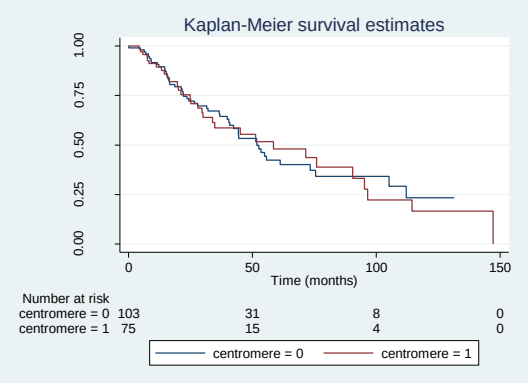
The overall survival of the cohort is shown below. 1 year survival is 87.6% (95% CI 82,92), 2 year 68.8% (95% CI 61,75), 3 year 58.6% (95% CI 51,66), 5 year 39.2% (95% CI 31,48) and 10 year 16.9% (95% CI 9,27).

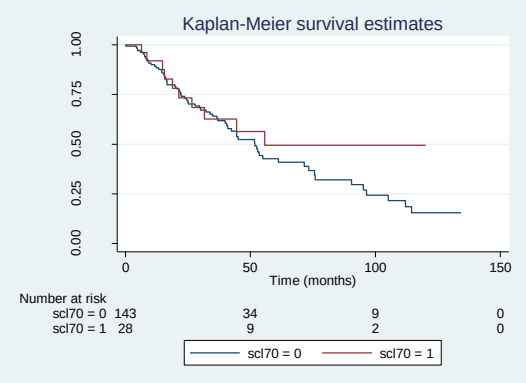


Autoantibody does not correlate with survival

Comparing survival in those with and without anti-centromere antibody shows no difference in survival (p=0.87), as does comparing patients with and without anti-Scl70 antibody (p=0.34).

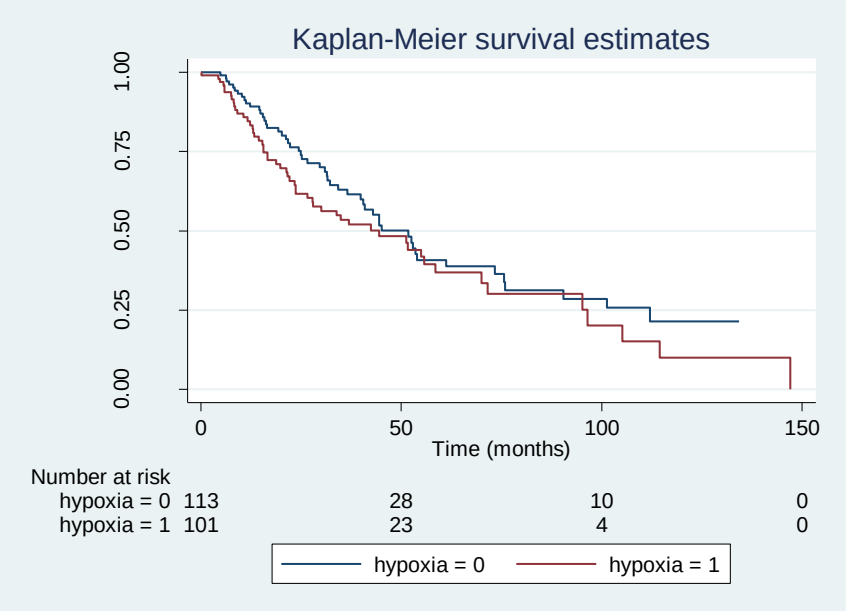
Kaplan-meier survival curves in patients grouped by antibody status





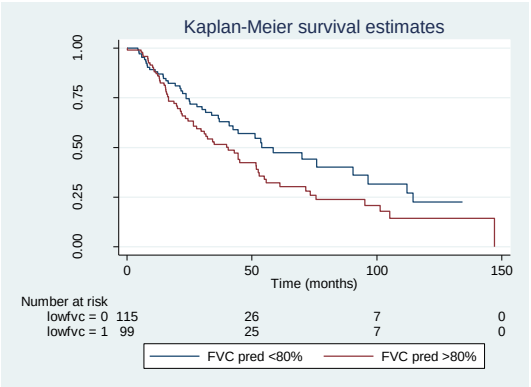
Oxygen Saturation does not correlate with survival

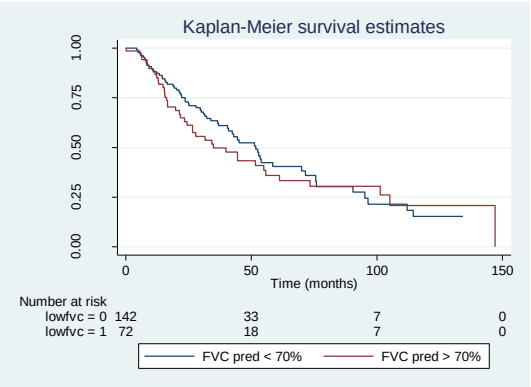
The median oxygen saturation was 95%, with 92% and 97% at the 25% and 75% quartiles respectively. Grouping patients into those above (SpO2≥95%) and below the mean (SpO2<95%) also does not show separation of the survival curves (p=0.20). Cox proportional hazards regression analysis showed that oxygen saturation does not predict survival (p=0.798).



FVC % predicted shows borderline association with survival

Cox regression shows that FVC % predicted as a continuous variable does not correlate with survival (p=0.40). The mean FVC is 81% and median is 82%. Defining low FVC as FVC pred < 80% gives a hazard ratio of 1.47 with borderline significance (p=0.052). Kaplan-Meier graph shows separation of survival curves, and log-rank analysis shows borderline significance (0.0503). Reducing the FVC threshold to 70% causes all association to be lost (p value by Cox 0.43, log-rank 0.43).





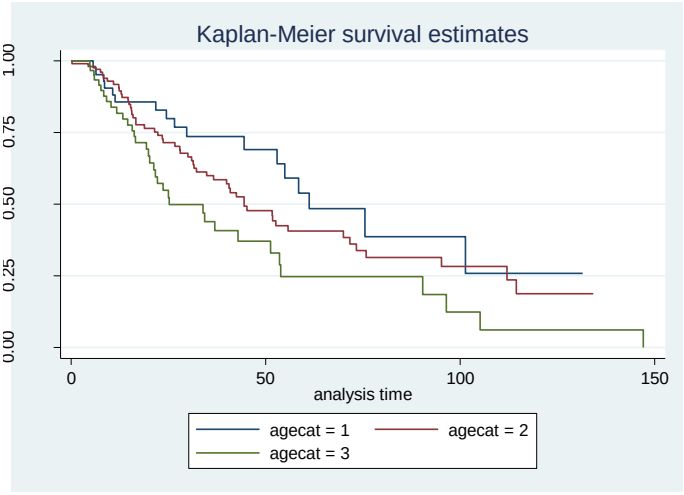
DL_{CO}% predicted is associated with Survival

Median DL_{CO} is 35.2% predicted. Cox proportional hazards shows a strong association between DL_{CO} % predicted as a continuous variable and survival (p<0.0005). Separating DL_{CO} at the

median value gives a good separation of survival curves (log rank p<0.00005). Cox analysis shows that those with lower than median DL_{CO} % predicted have a higher mortality than those above (Hazard ratio 2.27, p<0.0005).

Age Predicts Survival

Cox regression against age shows a significant relationship with survival (p=0.003). We formed a categorical value by splitting our sample into three groups by age: <50 (n=43), 50-70 (n=148) and >70 (n=38). The hazard ratio for age category is 1.6 (95% CI 1.1,2.2) with p=0.008.



Multivariable Cox Proportional Hazards Analysis

Multivariable Cox proportional hazards analysis was performed combining DL_{CO} % predicted with mean right atrial pressure (mRAP), mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR) and cardiac output (CO). mPAP and RAP fell out during this analysis (p=0.119 and p=0.126 respectively). Repeating the analysis with DL_{CO} % predicted, PVR and CO shows that CO also falls out (p=0.122). Thus, the best model is PVR and DL_{CO} % predicted (each with p<0.0005).

We explored use of DL_{CO} % predicted and PVR as categorical variables. We used the median values as cut offs (DL_{CO} median =35.2 %, PVR median = 453). This gave a hazard ratio of 2.00 for low DL_{CO} (p=0.001) and a hazard ratio of 1.58 for high PVR (p=0.03). There is no

significant interaction between DL_{CO} category and PVR category (Adding in a third variable representing DL_{CO} x PVR was not significant p=0.07).

Adding in age category (0 if<50, 1 if between 50-70 and 2 if >70) remained highly significant. So in the final model:

	Values	**Hazard Ratio (95% CI)**	**P Value**
DL_{CO} % category	0 if >40% 1 if 30-40% 2 if <30%	1.78 (1.4-2.3)	<0.0005
PVR category	0 if <350 1 if 350-650 2 if >650	1.56 (1.2-2.0)	0.001
Age category	0 if <50 1 if 50-70 2 if >70	1.58 (1.1-2.2)	0.01

A New Prognostic Score for Patients with SSc-PAH

We created categorical variables for DLCO and PVR by dividing each into three categories of equal sizes. We then rounded this to convenient numbers (DLCO cut-offs of 30.4,39.7 were rounded to 30,40 and PVR cut offs at 344, 635 were rounded to 350 and 650). We then created a risk score by adding the PVR score (starting from the lowest third), the DLCO score (starting from the highest third) and the Age score.

DL_{CO} % predicted	>40	30-40	<30
Score	0	1	2
PVR	**≤350**	**350-650**	**> 650**
Score	0	1	2
Age	**<50**	**50-70**	**>70**
Score	0	1	2

Risk score = DL_{CO} score + PVR score + Age score.

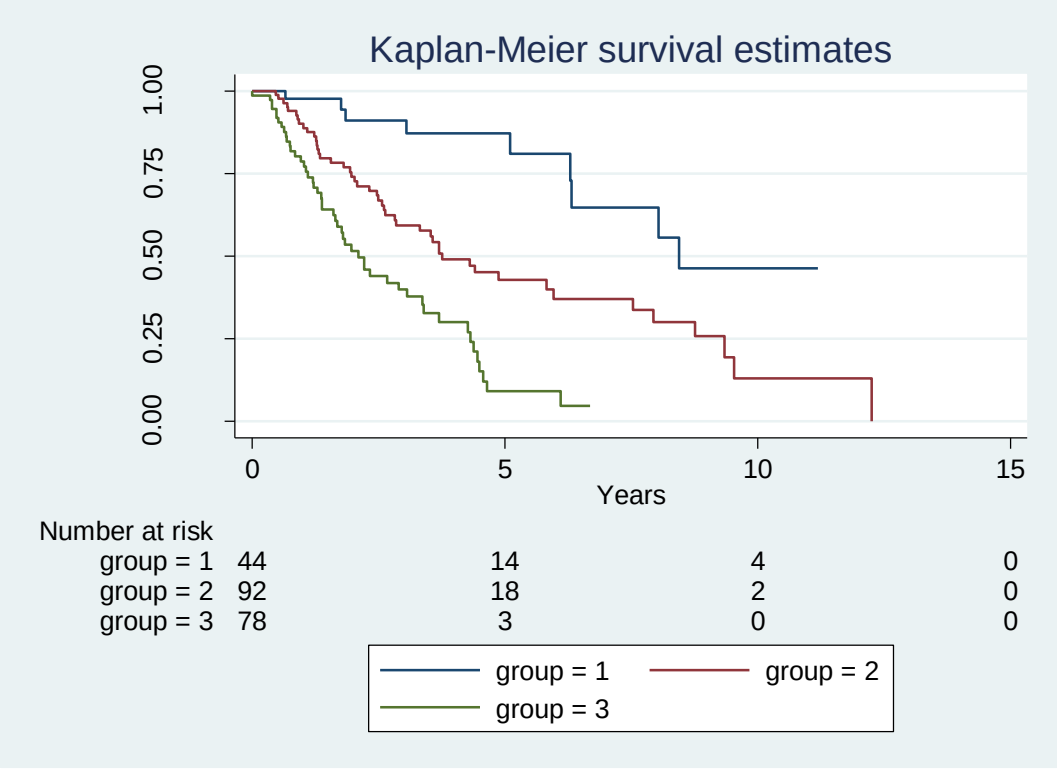
Survival by Score

This allows us to form three large prognostic groups. Group 1 have risk score of 0-1, group 2 have a risk score of 2-3, and group 3 have a risk score of 4-6.

The three groups have different survival curves. At 1 year p=0.15 for diff between Group 1 and Group 2, p=0.03 for diff between group 2 and group 3. By 3 years they are clearly distinct (p=0.006 for comparison of Group 1 to Group 2 and p=0.002 for comparison of Group 2 to Group 3). At 5 years (p=0.0005 for comparison of Group 1 to Group 2 and p=0.0001 for comparison of Group 2 to Group 3).

Each step increase in group is associated with a hazard ratio of 2.5 (95% CI 1.7,3.5) on Cox regression analysis (p<0.0005).

Group	Score	No. of patients	1 year survival	3 year survival	5 year survival	10 year survival	Median survival (months)
I	0-1	44	97.6% (84,100)	87% (69,95)	81% (58,92)	46% (19,70)	101.3 (75.6,n/a)
II	2-3	93	90% (81,95)	59% (47,70)	43% (30,55)	13% (3,30)	45.1 (34,72)
III	4-6	78	77% (65,85)	40% (27,52)	9% (3,21)	-	25.2 (19,41)
Overall	Mean 1.97	215	88% (82,92)	59% (51,66)	39% (31,48)	17% (9,27)	45.1



Conclusion

In patients with SSc associated PH, a simple equation incorporating age, gas transfer and pulmonary vascular resistance provides valuable prognostic information, and may help inform decision-making as to when, and for whom, to commence advanced PH therapies.

Survival scores in pulmonary arterial hypertension have been derived particularly from the French and American registries. The American Reveal registry score was initially derived in a large cohort of 2716 patients in the USA.[64] It came to some counterintuitive results, such as setting the threshold for risk from high pulmonary vascular resistance at an incredibly elevated level of 32 wood units, which is very rarely seen. They identified several features associated with poor prognosis, including portal hypertension, connective tissue disease, older males, renal insufficiency, and pericardial effusion on echocardiography. In addition, six minute walking distance, brain natriuretic peptide and diffusion of carbon monoxide correlated with survival. They have validated the risk score in newly diagnosed as well as established patients.[65] The risk score is not, however, scleroderma specific. The strength of our analysis is that it is derived in a scleroderma cohort and gives wide separation of groups. Independent validation would be

required, and further work should compare our score with the performance characteristics of the Reveal score in a scleroderma cohort.

Further Study

Work in this thesis is being taken forward in different directions. We have undertaken further analyses of our data, especially studying specific subgroups such as those with dermatomyositis, mixed connective tissue disease and myocardial involvement. Other planned analyses include comparing treatments with different classes of agents and the effect of drug therapy in a subgroup with interstitial lung disease.

The relationship between CT findings and pulmonary venoocclusive disease is being researched in a cohort of 200 scans, scored by two radiologists for features of PVOD and correlated with clinical findings.

We have set up a prospective 20 year research project for the study shortness of breath in patients with connective tissue disease with the Royal Brompton Hospital. This has full ethics approval. It will allow us to collect comprehensive data sets on patients prospectively in a real life setting over a prolonged time course.

We are planning a study of arrhythmias in systemic sclerosis and pulmonary hypertension using implanted loop recorders to detect arrhythmias prospectively in a cohort of patients with severe disease.

Finally, we have a growing program of basic research studying animal models of pulmonary hypertension and serum taken at the time of right heart catheterisation of patients with pulmonary hypertension.

Closing Remarks

Performing this research has undoubtedly taught me a huge amount. I feel it has given me a good grounding in medical statistics including in particular regression and survival analyses, as well as facing the limitations of retrospective data, missing data and the vicissitudes of daily life in clinical research. I have been clinically involved with patients with connective tissue disease, interstitial lung disease and pulmonary hypertension, and the research has all felt directly relevant to my work as a practicing physician.

Many of the most important questions in this area remain unanswered. We still do not understand why patients with scleroderma develop interstitial lung disease and pulmonary hypertension. One of the important clinical imperatives is to make an early diagnosis in the hope that we can impact on progression of these complications. Chapters 1-4 addressed issues relating to diagnosis. While physicians have long used clinical judgement to assess whether a particular patient is likely to have pulmonary hypertension, statistical analysis can refine clinical thinking by defining the risk associated with particular clinical features and by identifying subtle trends which can only be appreciated when a large number of patients is analysed at once. Thus for example, the fact that relatively small changes in oxygen saturation greatly enhance the significance of a reduced diffusion of carbon monoxide may well be helpful clinically. Efforts are underway currently to produce a guideline driven approach to diagnosis of pulmonary hypertension. It is important that statistical analyses should not trump clinical thinking but rather enhance it.

Some of the peculiarities of connective tissue disease associated pulmonary hypertension were explored next. In Chapter 5 we showed that patients with SLE tend to be younger than SSc patients, tend to have more responsive disease and better survival. Whether immunosuppression has a greater role in lupus patients is intriguing and is not yet satisfactorily addressed.

In chapter 6 we entered the discussion on pulmonary veno-occlusive disease and scleroderma. We reviewed the literature suggesting that there was a strong association between this rare variant of pulmonary hypertension and scleroderma and we analysed the radiological signs in a series of CT scans. We found that interlobular septal thickening were more common as patients age and that centrilobular nodules were associated with more severe pulmonary hypertension. Neither sign seemed to particularly correlate with pulmonary veno-occlusive disease, although they clearly can do so in some patients.

The final couple of chapters were devoted to prognosis in patients with systemic sclerosis. We first looked at the small group of patients with interstitial lung disease and pulmonary hypertension who were treated with immunosuppresants as well as pulmonary vasodilators. We found that KCO was closely associated with survival in these patients. It seemed in a single measure to best encapsulate the extent of both interstitial lung disease and pulmonary vasculopathy.

We then turned to survival in patients with systemic sclerosis and pulmonary hypertension and showed that DLCO % predicted is independently associated with survival, as is the patient's age.

In order to further the work represented in this thesis, we have set up a 20 year prospective study of breathlessness in connective tissue disease to capture prospectively the clinical stories of patients as they are investigated and treated for interstitial lung disease and pulmonary hypertension in particular.

Thank you for reading the thesis. I hope it has been of some interest.

Benji Schreiber

London, April 2013

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