Prediction and prognostication in interstitial lung disease associated pulmonary hypertension using baseline and longitudinal trends in non-invasive variables

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STATEMENT OF ORGINALITY

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ABSTRACT

Pulmonary hypertension (PH) commonly occurs in patients with interstitial lung disease (ILD) and is associated with worsening of symptoms and an adverse prognosis. The onset of PH is extremely difficult to predict due to the very similar symptomology of the two conditions and confounding of common screening tests for PH in patients with ILD. It is not clear what invasive and non-invasive variables predict mortality in ILD-PH patients, or whether existing mortality prediction tools used in ILD patients are valid in ILD-PH. I hypothesised that the prediction of PH occurring in ILD patients was possible using non-invasive screening tests, and that baseline and longitudinal change in non-invasive variables would predict mortality in ILD-PH patients.

The integration of echocardiographic, brain natriuretic peptide (BNP), pulmonary function tests and CT variables showed that prediction of PH occurring in ILD patients was possible, although false positives were common. Echocardiographic variables best correlated with invasive right heart catheter (RHC) pressures. A score was developed to predict severe PH using echocardiographic variables, and was effective even when blinding the most powerful predictor which is commonly unavailable in patients with ILD-PH.

CT is commonly employed in suspected ILD-PH patients to exclude co-existent pulmonary emboli and assess parenchymal disease progression. The right ventricle to left ventricle measured at CT pulmonary angiography was superior to both echocardiographic and RHC derived variables at predicting mortality.

The presence of PH confounds commonly used mortality prediction tools in ILD. A multi-modality mortality prediction model was developed to predict mortality using baseline demographics, lung function and ILD diagnosis. Longitudinal change in pulmonary function tests and BNP were shown to predict mortality. A longitudinal model using demographics and change in gas transfer was developed. External validation of the mortality prediction tools is necessary before its utility is demonstrated.

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ABBREVIATIONS

6MWD	Six-minute walk distance
Aa gradient	Alveolar arterial gradient
ANOVA	Analysis of variance analysis
Ao	Aorta
AUC	Area under the curve
BMI	Body mass index
BNP	Brain natriuretic peptide
BPHIT	Bosentan in pulmonary hypertension associated with fibrotic idiopathic Interstitial Pneumonia
CHP	Chronic hypersensitivity pneumonitis
CI	Cardiac index
CO	Cardiac output
COP	Cryptogenic organising pneumonia
COPD	Chronic obstructive pulmonary disease
CPI	Composite physiological index
CTD	Connective tissue disease
CTD-ILD	Connective tissue disease associated interstitial lung disease
CTPA	Computerised tomography pulmonary angiogram
DIP	Desquamative interstitial pneumonia
DM	Dermatomyositis
ERA	Endothelin receptor antagonist
ERS	European respiratory society

ESC	European society of Cardiology
FAC	Fractional area change
FC	Functional class
FVC	Forced vital capacity
GAP-Index	Gender age and physiology index
HP	Hypersensitivity pneumonitis
HR	Hazard ratio
HRCT	High resolution CT
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
ILD-GAP	Interstitial lung disease gender age physiology model
ILD-PH	Interstitial lung disease
IPAH	Idiopathic pulmonary arterial hypertension
IPF	Idiopathic pulmonary fibrosis
IVC	Inferior vena-cava
Kco	gas-transfer co-efficient
LA	Left atrium
LIP	Lympocytic interstitial pneumonia
LTOT	Long term oxygen therapy
LV	Left ventricle
MCTD	Mixed connective tissue disease
MMF	Mycophenolate
MPAD	Mean Pulmonary artery diameter

MPAD:Ao	Mean Pulmonary artery diameter to Aorta ratio
mPAP	Mean pulmonary artery pressure (at right heart catheter)
NO	Nitric oxide
NSIP	Non-specific interstitial pneumonia
OP	Organising pneumonia
OSA	Obstructive sleep apnoea
$PaCO_2$	Partial pressure of carbon dioxide
PAEC	Pulmonary artery endothelial cell
PAH	Pulmonary arterial hypertension
PaO_2	Partial pressure of oxygen
PDE-5	Phosphodiesterase type-5 inhibitors
PE	Pulmonary embolus
PFT	Pulmonary function tests
PH	Pulmonary hypertension
PM	Polymyositis
PPFE	Pleuro-parenchymal fibroelastosis
PR	Pulmonary regurgitation
PSAX	Parasternal short axis view
PVR	Pulmonary vascular resistance
QOL	Quality of life
RA	Right atrium
RBH	Royal Brompton Hospital
RB-ILD	Respiratory bronchiolitis associated interstitial lung disease

RHC	Right heart catheter
ROC	Receiver operator curve
RV	Right ventricle
RV:LV	Right ventricle to left ventricle ratio
RVPA	Right ventricle to pulmonary artery interaction factor
RVSD	Right ventricular systolic dysfunction
RVSP	Right ventricular systolic pressure
SLE	Systemic lupus erythematous
SS	Sjogrens syndrome
SScl	Scleroderma
TAPSE	Tricuspid annular plane systolic excursion
TLco	Gas transfer
TRv	Tricuspid regurgitation valve maximum
UIP	Usual interstitial pneumonia
VSB	Ventricular septal bowing

Chapter 1: Introduction

1.1 Interstitial Lung Disease

1.1.1 General introduction

Interstitial lung diseases (ILDs) is an umbrella term given to over 200 conditions which are grouped together because of their similarity in clinical presentation, radiological appearance and their pathophysiological effects. Although grouped under a single term, the population they affect, the rate of progression and response to treatment is highly variable both between different ILDs and within each specific diagnosis. The pathophysiological site of damage is the interstitium of the lung which is the area between the alveoli and pulmonary capillaries made up of connective tissue, fibroblasts and macrophages. In health, this layer allows rapid gaseous exchange. The ultimate trigger for the development of ILDs is specific to each cause and is thought to be an injury to the alveoli. The specific injury has many diverse causes, among them; smoking, asbestos fibres, proteins from bird feathers drugs and auto-immune disease from connective tissue. Damage to the alveoli results in healing and, where ongoing exposure continues, or the healing process is unchecked, ongoing damage and recruitment of inflammatory cells leads to thickening of the interstitium and irreversible fibrosis. This results in impaired gas exchange, ventilatory perfusion abnormalities and subsequent hypoxia. Dyspnoea manifests itself most symptomatically during exertion but as the disease progresses respiratory failure ensues at rest.

1.1.2 Classification

Accurately defining the cause of the underlying interstitial lung disease is of critical importance as it has implications on the treatment. The present classification of ILDs was

proposed in an international collaboration in 2001 (2002), and was further revised in 2013 (Travis et al., 2013).

The latest revision of the guidelines emphasised the importance of the multi-disciplinary team in addition to integrating patient demographic factors such as: age, smoking status, exposure history, other co-morbidities and rate of progression to assist in arriving at the correct diagnosis (Travis et al., 2013). The ILDs can be subdivided as:

- Idiopathic interstitial pneumonias
- ILD of a known association
- Granulomatous ILD
- Miscellaneous ILD

1.1.3 Idiopathic Interstitial Pneumonias

The recent revision of the Idiopathic interstitial pneumonias (IIPs) classified according to prevalence into “Major” and “Rare”, and where, despite MDT assessment, the diagnosis remains “Unclassifiable” (Travis et al., 2013).

The major IIP’s include:

- Idiopathic pulmonary fibrosis (IPF)
- Non-specific interstitial pneumonitis (NSIP)
- Cryptogenic organising pneumonia (COP)
- Respiratory bronchiolitis ILD (RB-ILD)
- Desquamative interstitial pneumonia (DIP)
- Acute interstitial pneumonia

The rare IIP's include:

- Lymphocytic interstitial pneumonia (LIP)
- Idiopathic pleuro-parenchymal fibroelastosis (PPFE)

Although RB-ILD is a pathological feature in smokers and DIP is almost universally caused by smoking they have been retained within the IIP category.

1.1.3.1 Idiopathic Pulmonary Fibrosis

IPF is a chronic, progressive ILD of an unknown cause and is the most common of the IIPs, occurring predominantly in older male adults and is associated with a usual interstitial pneumonia (UIP) type pattern at high resolution CT (HRCT) (figure 1.1) or pathologically at lung biopsy (Raghu et al., 2011).

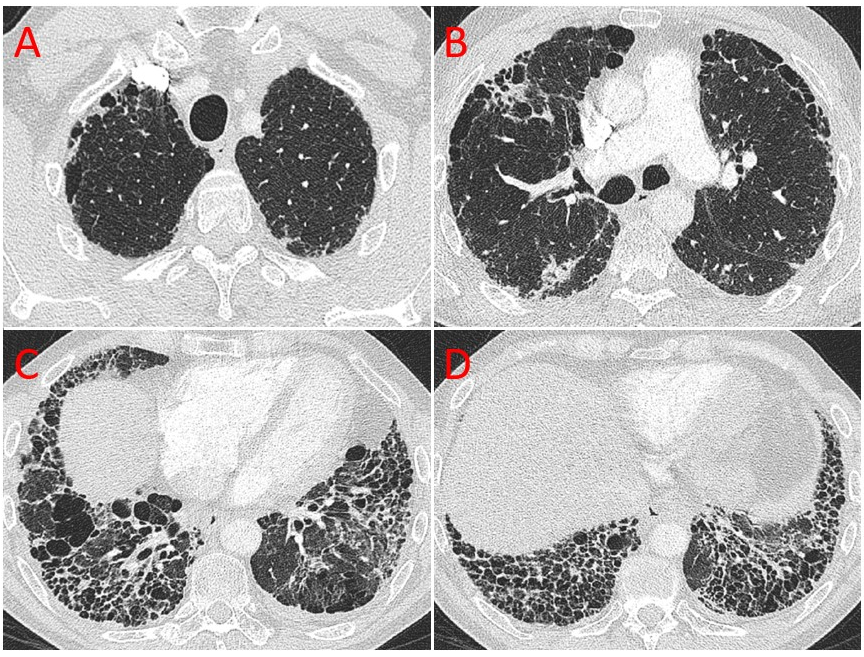


Figure 1.1. High resolution CT dicom's from a patient with Idiopathic pulmonary fibrosis from the ILD-PH cohort.

A – Apical thoracic level, B-C mid thoracic level, D basal thoracic level. This patient shows the typical features associated with a UIP pattern at HRCT, specifically: Subpleural and basal predominant distribution, loss of lung volume, irregular reticulation and honeycombing.

The true incidence and prevalence of IPF is difficult to ascertain due to differences in methodology and historical study's which were performed prior to the international consensus statement in 2000 on IPF(2000). The first study in the UK which evaluated a primary care database between 1991 and 2003 found an incidence of 4.6 per 100 000 per year (Gribbin et al., 2006), and a follow up study (2000 - 2009) using the same database showed an increasing incidence of 7.4 per 100 000/year which results in more than 5000 new cases per year in the UK (Navaratnam et al., 2011). The prognosis of IPF has historically been extremely poor with median survival from diagnosis of 2-3 years (Raghu et al., 2011). A severe reduction in forced vital capacity (FVC) <55% percent predicted at diagnosis is associated with a poor prognosis with a median survival of 27.4 months versus 55.6 months for individuals with an FVC >55% percent predicted (Nathan et al., 2011). Longitudinal decline in pulmonary function tests have been shown to be more accurate in prognosticating than the baseline value (Li et al., 2014). It is increasingly recognised that IPF is a heterogeneous disease with some patients experiencing slow progressive disease, others a much more rapidly progressive disease, and others still experiencing periods of stability punctuated by accelerated decline within acute exacerbations. IPF patients were previously treated with so called "Triple therapy" consisting of prednisolone, azathioprine and non-acetylcysteine. However, the landmark PANTHER-IPF randomised controlled clinical trial was terminated early as patients treated in this way were much more likely to die or require hospitalisation than patients treated with placebo (hazard ratio (HR):12.1 ,p=<0.001) (Idiopathic Pulmonary Fibrosis Clinical Research Network, 2012). Thankfully recent advances have been made and two antifibrotic agents (nintedanib and pirfenidone) are now available.

Both nintedanib and pirfenidone reduce lung function decline in mild to moderate disease and offer a survival benefit over placebo (Richeldi et al., 2014, King et al., 2014).

1.1.3.2 Non-specific interstitial lung disease

NSIP has only recently been acknowledged as a group of the IIPs and therefore its prevalence is poorly understood. NSIP is the most common pattern associated with connective tissue disease associated ILD (CTD-ILD), and following a diagnosis of NSIP a subsequent diagnosis of undifferentiated connective tissue disease or other connective tissue disease is as high as 9 – 33% (Park et al., 2009, Homma et al., 1995, Sato et al., 2006). The radiological features are shown in figure 1.2.

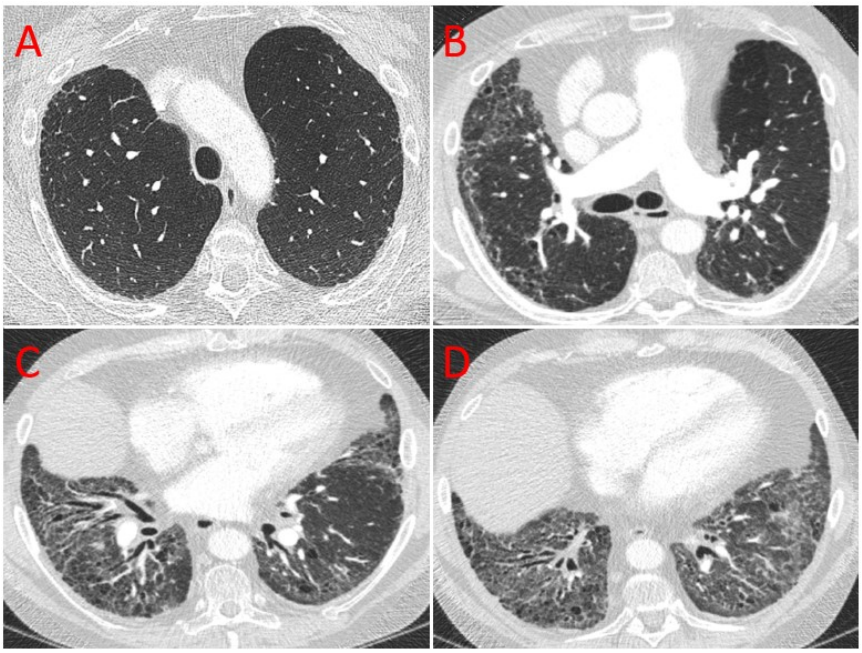


Figure 1.2. High resolution CT dicom's from a patient with Non-specific interstitial pneumonitis from the ILD-PH cohort.

A - Apical thoracic level, B mid thoracic level, C-D basal thoracic level. The HRCT demonstrates sub-pleural basilar predominant distribution. The mid-lower zone lung shows ground glass, irregular reticulation, and traction bronchiectasis. There is also sub-pleural sparing in panel B (as occurs in 20-50% of NSIP).

NSIP is more common in females, occurs in younger patients and approximately one half have never smoked (Belloli et al., 2016). Longitudinal disease behaviour in NSIP is poorly understood, and no randomised controlled clinical trials have been performed in NSIP to date. It has been suggested that when disease is mild then symptoms and pulmonary function tests (PFT) should be monitored (Belloli et al., 2016). If treatment is required, then immunosuppression with steroids initially followed by maintenance with azathioprine or mycophenolate is recommended. Prognosis is better than IPF, with an approximate mortality of 20% at 5 years (Park et al., 2009, Travis et al., 2008, Jegal et al., 2005).

1.1.3.3 Respiratory bronchiolitis-interstitial lung disease

Respiratory bronchiolitis occurs in all current tobacco smokers although rarely becomes symptomatic (Fraig et al., 2002). The development of dyspnoea and characteristic changes on HRCT (figure 1.3) suggests that RB-ILD is present. Smoking cessation is key to management and results in improvement in symptoms (Portnoy et al., 2007), and occasionally steroids are also necessary to improve resolution.

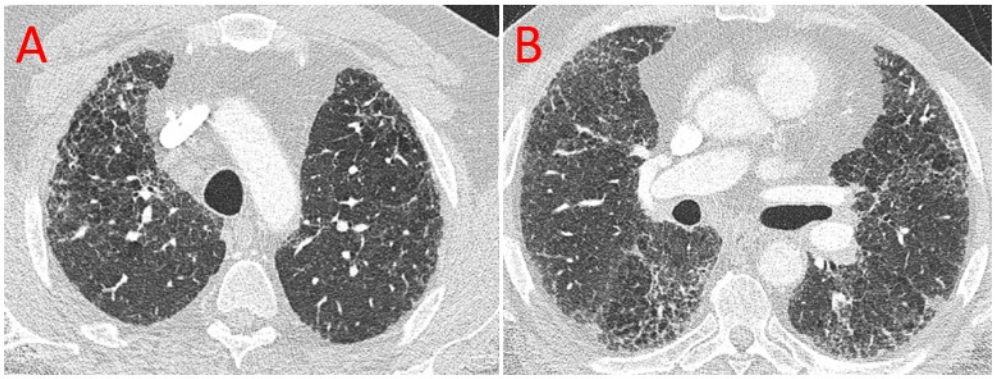


Figure 1.3. High resolution CT dicom's from a patient with Respiratory bronchiolitis interstitial lung disease from the ILD-PH cohort.

A - Apical thoracic level, B - mid thoracic level. The HRCT demonstrates centrilobular ground glass nodules, which dominate in the upper lobes admixed with emphysema and mild mosaic air trapping

1.1.5.2.2 Desquamative interstitial lung disease

Desquamative interstitial pneumonitis (DIP) is like RB-ILD although in DIP there is more generalised inflammation and DIP patients are usually more symptomatic. DIP is associated with smoking in more than 90% of cases, and untreated around two thirds of patients show disease progression, however spontaneous improvement has been reported (Carrington et al., 1978). The peak age of onset in DIP and RB-ILD is 30 – 50 years of age. Figure 1.4 shows a patient with DIP. Central to management if the patient is a smoker is smoking cessation, and corticosteroids usually halts further disease progression.

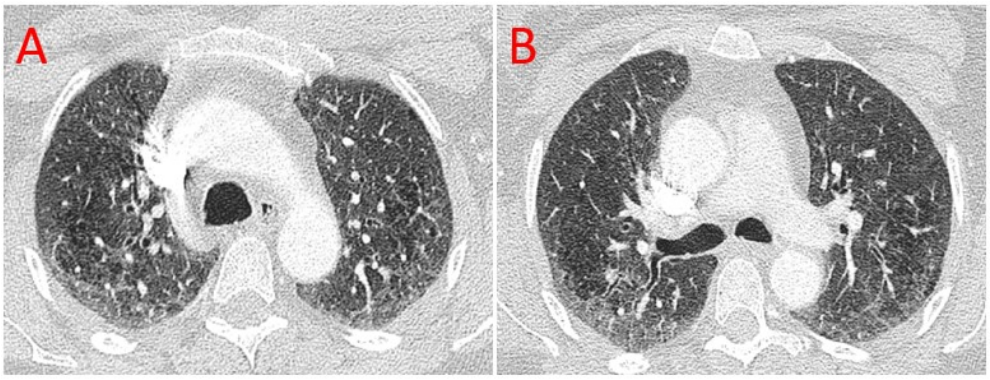


Figure 1.4. High resolution CT dicom's from a patient with desquamative interstitial pneumonitis from the ILD-PH cohort.

A - Apical thoracic level, B - mid thoracic level. The HRCT demonstrates patchy ground glass opacity with a sub-pleural predominance with emphysema / cysts within areas of the ground glass.

1.1.3.4 Pulmonary Langerhans cell histiocytosis

Although pulmonary Langerhans cell histiocytosis (Langerhans) is not an IIP due to its association with smoking I will discuss it briefly here. Over 98% of patients with Langerhans are current or ex-smokers (Schonfeld et al., 2012), and exposure to tobacco smoke has been

shown to proliferate Langerhans cells in tissue samples and bronchoalveolar fluid (Sholl et al., 2007). In early stage disease smoking cessation can be curative (Mogulkoc et al., 1999), although in advanced disease progression occurs and co-existent pulmonary hypertension has been seen in more than 75% (Fartoukh et al., 2000, Chaowalit et al., 2004b).

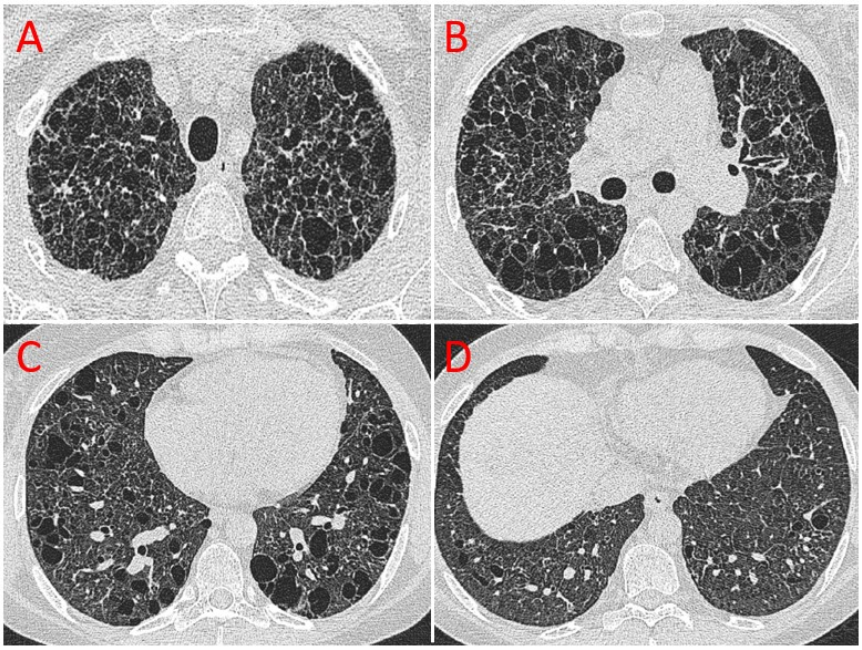


Figure 1.5. High resolution CT dicom's from a patient with Langerhans cell histiocytosis from the ILD-PH cohort.

A - Apical thoracic level, B - mid thoracic level, C-D basal thoracic level. This HRCT demonstrates advanced Langerhans cell histiocytosis with irregular shaped cysts (Panel A-C) which show an upper lobe predominance and sparing of the costophrenic angles (Panel D).

1.1.3.5 Cryptogenic organising pneumonia

Although there are many known causes of organising pneumonia (OP), in 50% of cases the underlying trigger remains unknown; this is referred to as cryptogenic OP (COP). The histological hallmark of COP is plugs of granulation tissue within the lumen of the bronchioles, alveolar ducts and peri-bronchiolar alveoli (Beardsley and Rassl, 2013). Clinical

presentation is usually associated with systemic symptoms, cough and dyspnoea. Radiological abnormalities include migratory consolidation on chest radiograph and patchy consolidation and ground glass in a sub-pleural, peri-bronchiolar or bandlike distribution at HRCT. The prognosis of COP (without features of fibrosis) is usually excellent with rapid resolution with oral prednisolone (King and Mortenson, 1992), which can usually be tapered over a number of weeks to months although relapse is common. COP can also occur alongside NSIP which makes progression more likely (and makes a co-existent CTD such as polymyositis and anti-synthetase syndrome more likely) (Travis et al., 2013).Where steroid therapy cannot be weaned then treatment with a steroid sparing agent such as azathioprine may be necessary (Cottin and Cordier, 2012).

1.1.3.6 Idiopathic lymphoid interstitial pneumonia

LIP usually occurs alongside a connective tissue disease (CTD) (particularly rheumatoid arthritis, Sjogrens syndrome or HIV) and is characterised by dense lymphocytic interstitial infiltrate. True idiopathic LIP is very rare (Nicholson, 2002). Peak age of occurrence is between 40 and 70 years and the majority of those affected are women (Swigris et al., 2002), and presentation with cough and slowly progressive dyspnoea. At HRCT ground glass opacities and small nodules occur in a peri-lymphatic distribution with thickened broncho-vascular bundles in a patchy or diffuse distribution with cysts (Honda et al., 1999, Ichikawa et al., 1994). The diagnosis of LIP requires a surgical lung biopsy and if confirmed the patient should be carefully screened for other causes and if an associated condition is found then treatment is focused on the underlying cause (Tian et al., 2012). Corticosteroid therapy usually results in improvement in 50 to 60% of patients (Swigris et al., 2002), although there

is a large degree of variability in the prognosis of LIP with 33 to 50% of patients dying within 5 years.

1.1.3.7 Pleuro-parenchymal fibroelastosis

PPFE is a relatively recently described clinical entity (Reddy et al., 2012), and is characterised by fibrosis occurring at the pleural and sub-pleural lung, predominantly affecting the upper lobe. PPFE tends to occur at an earlier age than IPF and does not appear to be associated with smoking and shows no gender predominance. In the early stages of PPFE bilateral apical pleura is irregular and thickened, and subsequently reticular and nodular opacities occur which cause elevation of the hilum. PPFE can occur in isolation or can occur with a UIP type pattern of IPF or chronic hypersensitivity pneumonitis (Reddy et al., 2012). The clinical course of PPFE is not well understood and varies according to its other associations, where it occurs alongside basal UIP like pattern if often follows an IPF like disease course.

1.1.4 Connective Tissue Disease associated Interstitial Lung Disease

ILD complicating CTD is common and its subtype and prognosis is strongly linked to the underlying CTD. Often patients initially diagnosed with an ILD are found to have CTD like features and serological testing and clinical symptoms confirms CTD. This has important implications on both prognosis and treatment options.

	Connective tissue disease					
	SSCL	**RA**	**SS**	**MCTD**	**PM/DM**	**SLE**
Occurrence of ILD	Likely	Common	Possible	Common	Likely	Unusual
ILD pattern	NSIP (80-90%) UIP (10-20%)	UIP (50-60%) NSIP,OP,DIP	NSIP (28-60%) LIP 20%	NSIP	NSIP,OP, UIP, DAD	
Occurrence of PH	Likely	Unusual	Unusual	Likely	Unusual	Unusual
PH Classification	PAH, Group 3			PAH, Group 3		

Table 1.1. Features of lung involvement in connective tissue disease

Abbreviations: SSCL – Scleroderma, RA – rheumatoid arthritis, SS – Sjogrens syndrome, MCTD – Mixed connective tissue disease, PM/DM – Polymyositis / Dermatomyositis, SLE – Systemic Lupus erythematous, NSIP – Non-specific interstitial pneumonitis, UIP – Usual interstitial pneumonia, OP – Organizing pneumonia, DIP – Desquamative interstitial lung disease, LIP – Lymphoid interstitial pneumonia, DAD, Diffuse alveolar damage, PAH – Pulmonary arterial hypertension, Adapted from (Mathai and Danoff, 2016)

1.1.4.1 Scleroderma

Scleroderma (SScl) has a very high risk of ILD, and patients with diffuse cutaneous or anti Scl-70 (anti-topoisomerase antibodies) are at a higher risk. In a cohort made up of 3656 SScl patients (EUSTAR) 60% of SCL-70 positive patients had evidence of ILD versus 21% of patients with anti-centromere antibodies (Walker et al., 2007). SScl can present with several different patterns at HRCT (Figure 1.6). Prognosis in SScl associated ILD is poor. Patients with a UIP type pattern (median survival – 3 years) have a worse prognosis than patients with an NSIP type pattern (median survival – 15 years) (Bouros et al., 2002).Older age, worse lung function and a greater ILD extent at HRCT also predict mortality and disease progression (Winstone et al., 2014).

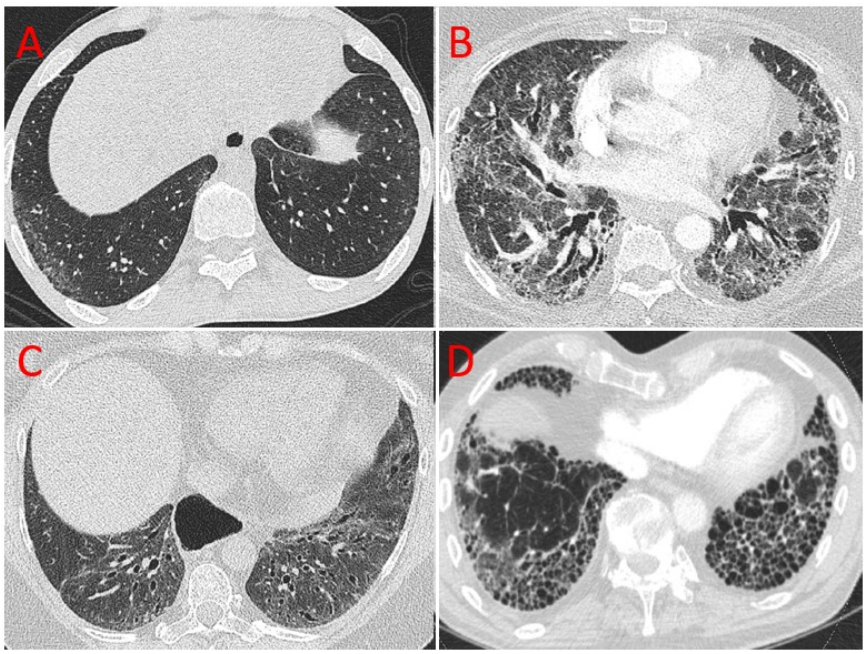


Figure 1.6. High resolution CT dicom's from four different patients with Scleroderma from the ILD-PH cohort.

A - demonstrates basal ground glass opacity without features of fibrosis, B - Mid thoracic level in a different patient demonstrates irregular reticulation ground glass and traction bronchiectasis, C- Oesophageal dilatation is seen in panel C, D - A usual interstitial pattern can also occur in scleroderma associated ILD.

1.1.4.2 Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is common affecting 0.5 – 1% of the US population (Helmick et al., 2008), the joints of the hand are most commonly affected. Approximately 40% of patients with RA will have some form of lung disease. ILD is present in 19% of randomly selected patients with RA (Dawson et al., 2001). A UIP pattern is the most common pattern at HRCT, although NSIP, organising pneumonia and follicular bronchiolitis can also occur. ILD occurring in association with RA unfortunately has a poor prognosis and accounts for 10% of deaths (Olson et al., 2011).

1.1.4.3 Polymyositis / Dermatomyositis and Anti-synthetase syndrome

ILD can occur in the setting of polymyositis (PM) and dermatomyositis (DM), and is more prevalent still in antisynthetase syndrome. Antisynthetase syndrome diagnostic criteria require one or more of the anti-synthetase antibodies (Anti-Jo-1 is most common), with ILD and one of the following: inflammatory myopathy, polyarthritis, Raynaud's and mechanics hands (drying and cracking of the skin on the radial side of the first digit and hands). The most common pattern seen on CT is NSIP. Organising pneumonia can also occur in isolation although commonly occurs with NSIP (figure 1.7).

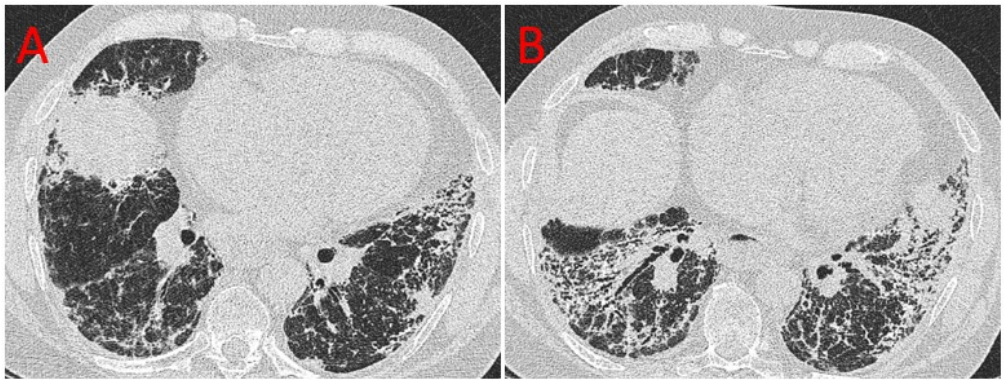


Figure 1.7. High resolution CT dicom's from the one patient with antysynthetase syndrome from the ILD-PH cohort.

A & B - Shows a NSIP pattern with Organising pneumonia also present in the right lower lobes

1.1.4.4 Mixed connective tissue disease

Mixed connective tissue disease (MCTD) is defined be the presence of U1 RNP (Sharp et al., 1972). MCTD has overlapping features of the common CTDs particularly SScl, Lupus and PM. ILD is common, a longitudinal cohort found that 53% of 201 patients over a median follow up of 12.5 years developed ILD (Szodoray et al., 2012). At HRCT NSIP and UIP are most common, although LIP and OP can also occur.

1.1.4.5 Systemic lupus erythematous

The lungs are affected in 33-50% of patients with systemic lupus erythematosus (SLE). Although, ILD is less common than in the other CTD's as it only affects between 1-15% of patients (Mittoo and Fell, 2014). ILD is more common in patients with overlap syndromes of SLE with anti-U1 RNP antibodies, sclerodactyly, and Raynaud's phenomenon increasing the likelihood of ILD (ter Borg et al., 1990). Acute presentation causing fulminant respiratory failure in otherwise well patients has been reported; acute lupus pneumonitis has a mortality approaching 50% (Matthay et al., 1975).

1.1.4.6 Sjögren's Syndrome

Sjögrens disease causes dysregulation of the lacrimal and salivary glands, dry eyes and dry mouth are hallmarks of the disease. Autoantibodies anti-SSA and anti SSB are usually present. The most common pattern at HRCT is NSIP and LIP (figure 1.8). OP and UIP can also occur but are much less common (Parambil et al., 2006). The incidence of ILD increases as the duration of Sjögren's syndrome increases (Flament et al., 2016).

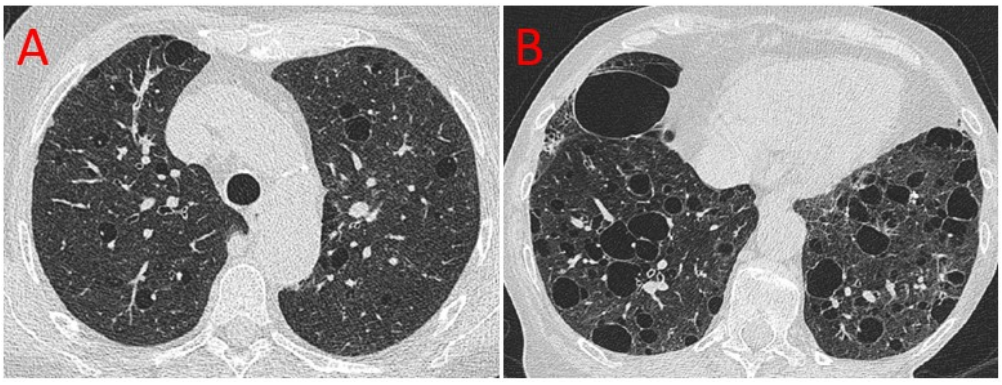


Figure 1.8. High resolution CT dicom's from a patient with Sjögrens syndrome from the ILD-PH cohort.

A - Mid thoracic level, the cysts are normally round and thin walled and less numerous than Langerhans cell histiocytosis, B - The cysts of LIP involve all lung regions (unlike Langerhans cell histiocytosis which usually spares the bases).

1.1.5 Treatment of CTD-ILD

When ILD occurs in CTD, it impacts on symptoms and increases mortality especially when it occurs with pulmonary hypertension. Despite this there are very few prospective randomised controlled clinical trials to guide therapy, and treatment is based upon previous experience and retrospective cohort studies. In general, supportive measures including oxygen, treatment and prevention of infections, gastroesophageal reflux, sleep disordered breathing which apply in IIP also apply in CTD-ILD. Corticosteroids are nearly always the initial immunomodulation of choice in CTD-ILD, although doses of more than 20mg should not be exceeded in Scleroderma due to the risk of precipitating renal crisis (Iudici et al., 2013). Cyclophosphamide has the largest evidence base in Scleroderma and was associated with small but significant improvements in FVC when (Tashkin et al., 2006), oral cyclophosphamide was compared with placebo. A further study evaluated IV cyclophosphamide followed by azathioprine and found a non-significant trend toward improvement (Hoyles et al., 2006). The most recent Scleroderma Lung Study II compared oral mycophenolate (MMF) over 2 years with one year of oral cyclophosphamide, and found that both improved lung function although neither was superior, although MMF was better tolerated (Tashkin et al., 2016). Other immunomodulators are commonly used particularly methotrexate (RA / PM / DM), azathioprine (SScl / PM / DM), and MMF (SScl / PM / DM / RA). Other biological immunomodulating agents such as rituximab (monoclonal antibody causing B cell depletion for 6 to 9 months) have increasingly been used, a randomised controlled clinical trial comparing cyclophosphamide versus rituximab is underway (RECITAL STUDY).

1.1.6 Sarcoidosis

Sarcoidosis is a multisystem inflammatory disorder characterised by non-necrotising granuloma deposition, which is more common in young adults. Despite multiple studies the causative agent of sarcoidosis remains elusive although it is thought that sarcoidosis results from exposure to an infectious / non-infectious agent together with immune dysregulation occurring in genetically susceptible individuals (Semenzato, 2005). Sarcoidosis is known as the “great mimicker”, and therefore clinical presentation is highly variable. Patients with pulmonary sarcoidosis develop cough, dyspnoea and systemic symptoms, however many cases are asymptomatic with spontaneous resolution. Patients with isolated hilar lymphadenopathy have an excellent prognosis with spontaneous resolution in 60% to 90% at 5 years, which compares to 10 to 20% in patients with parenchymal lung disease (Hillerdal et al., 1984). The HRCT findings in sarcoid are discussed in figure 1.9. Patients with extra pulmonary disease affecting the heart, eye or brain all require treatment, and patients with pulmonary disease should be monitored; those with extensive disease or progression in symptoms / deterioration in imaging or pulmonary function tests should be treated. Treatment is with corticosteroids and most show response to prednisolone although a relapse does occur in 20% to 74% of patients following withdrawal of prednisolone (Gottlieb etal.,1997).

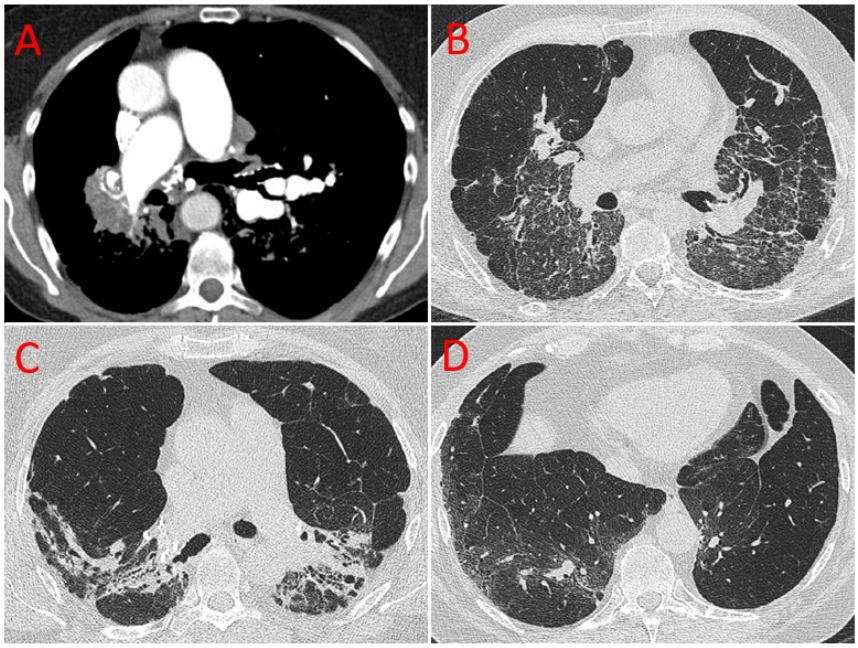


Figure 1.9. High resolution CT dicoms from three different patients with Sarcoid from the ILD-PH cohort.

A - demonstrates enlarged partially calcified mediastinal lymph nodes, a common finding in chronic pulmonary sarcoidosis, B - Mid thoracic level in a different patient demonstrates the peri-lymphatic pattern of nodular formation in Sarcoidosis with peri-bronchovascular, sub-pleural interlobular and centrilobular nodules, C - mid thoracic level and D - basal thoracic level in the same patient demonstrates the predominant upper lobe nature of Sarcoidosis again with peri-bronchovascular distribution.

1.1.7 Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is caused by the inhalation of an antigen to which the individual is sensitized, with a hyper-responsive reaction which results in lung parenchyma and airway damage. There is a wide variation between exposure to antigens causing HP and the actual development of symptomatic HP; indeed the presence of an antigen specific serum IgG antibodies does not imply HP and commonly occur in exposed individuals (Cormier et al., 2004). Therefore, it is thought that as in sarcoidosis there is an additional interaction between environment and genetic factors for HP to propagate. Avian antigens

(present in bird feather and bird droppings), and microbiological agents (fungi and mycobacteria) are the most common implicated antigens (Glazer, 2015). Acute HP can occur in response to high antigen exposure with acute cough, dyspnoea, and constitutional symptoms. Recovery is normally complete but symptoms recur on re-exposure, and treatment is not normally necessary if antigen avoidance is possible (Selman et al., 2012). Subacute or chronic HP occurs with prolonged low-level exposure and presentation is much more insidious with the latency between exposure and development of symptoms varying between months and many years (Morell et al., 2008). The combination of typical findings of chronic HP at HRCT and the appropriate clinical setting is diagnostic of HP (figure 1.10) (Elicker.B, 2013).

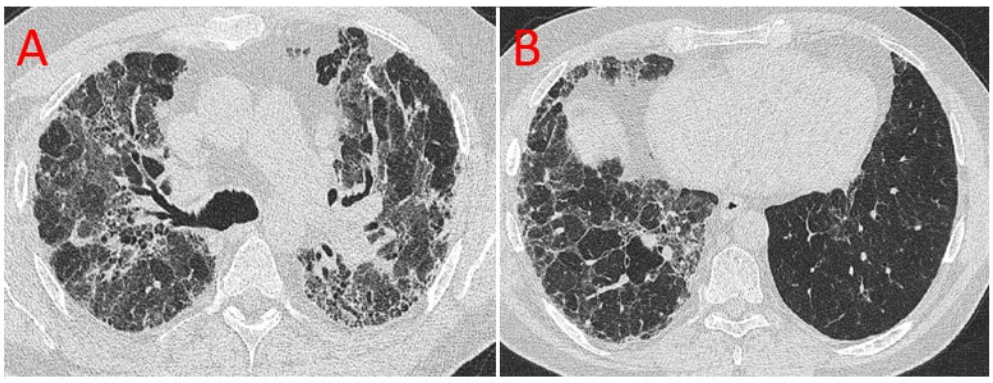


Figure 1.10. High resolution CT dicom's from a patient with Chronic hypersensitivity pneumonitis from the ILD-PH cohort.

A - Mid-thoracic level demonstrates mid-zone distribution with prominent ground glass, lobular mosaic perfusion abnormality, patchy bilateral irregular reticulation and traction bronchiectasis, B - Basal level confirms the predominant distribution is mid and upper-zone, and there is further lobular mosaic change and irregular asymmetric reticulation. No honeycombing is present.

Removal of the causative agent in chronic HP may not prevent further progression and treatment with corticosteroids is usually necessary. A recent retrospective study showed

that treatment with either MMF or azathioprine resulted in a small but statistically significant improvement in gas transfer (Morisset et al., 2017).

1.2 Pulmonary Hypertension

1.2.1 Definition and clinical classification of pulmonary hypertension

Pulmonary hypertension (PH) is defined by an increase in the mean pulmonary artery pressure (mPAP) ≥25mmHg measured at rest by right heart catheterisation. PH is further subdivided into pre-capillary (where mPAP is ≥25mmHg and pulmonary capillary wedge pressure (PCWP) ≤15mmHg) or post capillary (where mPAP is ≥25mmHg and PCWP >15mmHg) (Galie et al., 2016). Post capillary PH includes all patients in group 2 (PH associated with left-sided heart disease). Pre-capillary PH includes all patients in groups 1, 3, 4 and 5.

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1''. Persistent pulmonary hypertension of the new-born (PPHN)

2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Table 1.2. **Updated classification of pulmonary hypertension (5TH WSPH Nice 2013)**

Since the second World Symposium on PH held in Evian in 1998 (Simonneau et al., 2004) PH was classified into 5 groups where individual diagnoses shared similar haemodynamics, pathology and management. The updated classification adapted from (Simonneau et al., 2013) is shown.

Importantly pulmonary arterial hypertension (PAH, group 1) (as opposed to PH) is characterised by the presence of pre-capillary PH and a pulmonary vascular resistance > 3

Wood unit in the absence of other causes of pre-capillary PH (Galie et al., 2016). Although there are many different causes in group 1, all forms of PAH in this group share similar clinical presentation and pathological changes.

1.2.2 Clinical presentation of PAH

Symptoms of pulmonary hypertension are non-specific and there is often a long period between development of symptoms and diagnosis. Initially symptoms are precipitated by exertion and related to RV dysfunction induced by pulmonary hypertension. Shortness of breath on exertion, a declining exercise tolerance and general symptoms of weakness and fatigue are common. As the disease progresses and RV failure develops peripheral oedema, palpitations, angina like chest pain and syncope can occur. As PH has many causes its presentation is modified by the underlying cause with PH often found later in Group 3 patients where these symptoms are often attributed to lung disease. Auscultation of the precordium may demonstrate an accentuated pulmonary component of the second heart sound, pan-systolic murmur of tricuspid regurgitation, or a third heart sound. Elevation of the jugular venous pressure, hepatomegaly, ascites and peripheral oedema are late signs of PH.

1.2.3 Treatment of PAH

In general, the treatment of PH can be separated into the following categories (Specific vasodilator therapy is only recommended in groups 1, 4, and 5, and the treatment of group 3 patients is discussed in more detail later);

- Supportive therapy
- Specific vasodilator therapy

- Evaluation and modification to vasodilator therapy.

1.2.3.1 Supportive therapy

Supportive therapy of patients with PH applies to all clinical groups of PH and includes;

- Promotion of physical activity and supervised rehabilitation
- Annual influenza vaccination and pneumococcal vaccination
- Careful planning of elective surgery
- Psychosocial support
- Long term oxygen therapy (where PaO2 <8Kpa)
- Optimal diuretic regimens
- Correction of Iron deficiency

1.2.3.2 Calcium channel blockers

Treatment with Calcium channel blockers (nifedipine, diltiazem and amlodipine) is only appropriate for patients with idiopathic PAH who have a positive response to vasodilator testing at RHC.

1.2.3.3 Endothelin receptor antagonists (ERA)

Endothelin-1 (ET-1) is a potent vasoconstrictor and promoter of vascular smooth muscle cell proliferation; its role in the pathogenesis of pulmonary arterial hypertension (Giaid et al., 1993), (Galie et al., 2004). ERAs can cause hepato-toxicity and therefore monthly liver function is testing is necessary and they should not be used in patients with mild to severe hepatic impairment. ERAs have been shown to; improve functional class, prevent functional class deterioration, improve invasive haemodynamics, and improve patients exercise capacity in patients in functional class II and III PAH (Liu et al., 2013). Macitentan has also

been shown to significantly reduce morbidity and mortality in patients with PAH (Pulido et al., 2013).

1.2.3.4 Phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators

Phosphodiesterase type 5 inhibitors (PDE-5) leads to vasodilation through the nitric oxide / cyclic guanosine monophosphate pathway and demonstrates antiproliferative effects (Tantini et al., 2005). PDE-5 inhibitors (sildenafil and tadalafil) inhibit the degradation of cyclic guanosine monophosphate which is synthesized by soluble guanylate cyclase in response to nitric oxide (NO), leading to pulmonary vasodilation. In PAH sildenafil has been shown to improve invasive haemodynamics and six-minute walk distance (6MWD), although was not shown to increase the time taken to clinically deteriorate (Galie et al., 2005). Tadalafil has been shown to improve 6MWD and the highest dose increased the time to clinical worsening (Galie et al., 2009). Common side effects include headache, flushing and epistaxis.

1.2.3.5 Prostacyclin analogues and prostacyclin receptor agonists

Prostacyclin is a potent vasodilator produced by endothelial cells, which also inhibits platelet aggregation and is antiproliferative (Jones et al., 1995). Prostacyclin and its analogues are members of the prostanoid family. Prostacylin inhibits platelet activation and acts as a potent vasodilator. PGI_2 also displays anti-inflammatory and anti-proliferative properties. Prostanoid therapy can be provided by either continuous intravenous infusion (epoprostenol, iloprost), intermittently inhaled via nebuliser (iloprost), and recently an oral formulation has become available (selexipag). IV epoprostenol was the first specific drug therapy approved in PAH and has been shown to improve haemodynamics, quality of life

(QOL), and survival (Barst et al., 1996). The recently approved oral selexipag was shown to reduce time to primary endpoint (death or complication related to PAH) (Sitbon et al., 2015).

1.2.4 Group 3 PH

Mild elevation in mean pulmonary pressure is common in patients with chronic respiratory disease and has been defined in the recent PH guidelines (table 1.3).

Terminology	Right heart catheter haemodynamics
Chronic lung disease without PH	mPAP <25mmHg
Chronic lung disease with PH	mPAP ≥25mmHg
Chronic lung disease with severe PH	mPAP ≥ 35mmg, or mPAP ≥25mmHg in the presence of a low cardiac output (Cardiac index <2.5L/min, not explained by other causes)

Table 1.3. Definition of pulmonary hypertension due to lung disease

Abbreviations: mPAP - Mean pulmonary pressure, adapted from (Galie et al., 2016)

1.2.4.1 Pathophysiology of ILD-PH

The current classification of PH associated with ILD is based on perceived common pathophysiology leading to the development of PH; it stresses the presence of lung fibrosis and hypoxia being the major contributory factors (Galiè et al., 2015). There are several criticisms of this simplified view: Firstly, although ablation of pulmonary vessels ("vascular rarefaction") is clearly important, there is no direct relationship between the level of fibrosis, demonstrated by pulmonary function tests (Nathan et al., 2007, Hamada et al., 2007) or CT parameters (Zisman et al., 2007a). Secondly, most patients with ILD who

develop PH are not sufficiently hypoxaemic to explain the increased pulmonary arterial pressure. The mechanism of PH development in group 3 is thought to relate to the following:

- Mechanical factors, rarefaction and angiogenesis
- Hypoxic vasoconstriction
- Pulmonary vascular remodelling
- Contribution of other co-morbid conditions (thromboembolic disease, sleep disordered breathing, left heart disease)

1.2.4.2 Mechanical factors and rarefaction and angiogenesis

Pulmonary capillaries lie adjacent to alveolar walls, and therefore are subject to mechanical forces which influence pulmonary blood flow and pulmonary vascular resistance (PVR) (Lumb, 2010). Where hyper-expansion occurs increased pressure is transmitted to the pulmonary capillaries which results in a reduced size of the capillary lumen which increases PVR (Harris et al., 1968). Similarly, in ILD a reduction in lung volume causes direct compression of pulmonary capillaries increasing PVR (Howell et al., 1961). The observation that vascular remodelling occurred in pulmonary fibrosis was first made in 1963 by Turner-Warwick who demonstrated anastomoses between the systemic and pulmonary micro-vasculature associated with neovascularization within areas of fibrosis (Turner-Warwick, 1963), while other studies have reported an overall reduced vascular density (Renzoni et al., 2003). Subsequently, it has been accepted that both phenomena occur in different areas of the same lung (Ebina et al., 2004, Gregory P. Cosgrove et al., 2004). Increased vascularity is seen at the interface between fibrosis and normal lung parenchyma, and decreased

vascularity within areas of fibrosis with abnormally dilated vessels within areas of honeycombing (Ebina et al., 2004). Indeed, new vessel formation has been shown to be maladaptive with increased irregularity and dilatation (Kwon et al., 1991), and lacking an elastin layer which may (Ebina et al., 2004), contribute to an increase in PVR.

1.2.4.3 Hypoxic vasoconstriction and remodelling

In the systemic circulation vasodilatation occurs rapidly in the presence of hypoxia to maintain local tissue perfusion, whereas in the pulmonary circulation it triggers vasoconstriction to divert blood flow preferentially to maintain ventilation and perfusion and optimize gaseous exchange. Pre-capillary arterioles are the site of greatest contribution to increased PVR. Smooth muscle cells contract in response to hypoxia, and medial smooth muscle cell proliferation and thickening is the major contributor to increased PVR. The pulmonary artery endothelial cell (PAEC) is the innermost layer of the pulmonary artery and is crucial in regulating changes in the pulmonary vasculature in response to hypoxia. The intimal layer can detect changes in oxygenation, pulmonary blood flow and pressure, and interacts with circulating factors. The intimal layer shows the least remodelling of the three layers of the vessel wall, and changes include hypertrophy of the PAEC, sub-endothelial oedema, and fibrosis, and occasionally longitudinal muscle formation (Heath et al., 1981, Heath et al., 1990, Meyrick and Reid, 1980). The PAEC responds to hypoxia by inducing vasoconstriction through decreased production of and or activity of prostacyclin and NO, and through increasing levels of ET-1, serotonin and leukotrienes (Aaronson et al., 2002, Faller, 1999). In-vitro studies have demonstrated that PAEC's respond to hypoxia by the synthesis and release of pro-inflammatory (IL-1, IL-6, IL-8), pro-mitogenic (VEGF-1, ET-1,

thromboxane, PDGF-B) and cell adhesion molecules (vascular cell adhesion molecule, intercellular adhesion molecule, P-selectin) (Ten and Pinsky, 2002, Aaronson et al., 2002). Pulmonary artery smooth muscle cells which exist in the medial layer are thought to be responsible for the thickening of the muscular layer through hypertrophy and increased proliferation which results in a decreased compliance of the larger pulmonary vessels (Hunter et al., 2011). The muscularization of previously non-muscular segments and hypertrophy of partially muscular segments are thought to occur due to migration and proliferation of smooth muscle along the non-muscularized segments (Sheikh et al., 2014). The outermost layer of the vessel the adventitia undergoes substantial thickening due to an increase in collagen and protein deposition in the extracellular matrix, expansion of the vasa vasorum and proliferation of resident fibroblasts and activation of resident progenitor cells and further recruitment of circulating and immune and progenitor cells (Stenmark et al., 2013). However, the fact that oxygen therapy does not reverse the increase in PVR (Lumb, 2010), and the fact that PH occurs in patients with minimal hypoxia suggests that other mechanisms are important.

1.2.4.4 Pulmonary Vascular Remodelling

Pulmonary vascular remodelling results in structural changes, which decreases vascular distensibility and compliance. Hypoxic pulmonary vascular remodelling will occur if alveolar hypoxia is prolonged or permanent, but further to this, there is heterogeneity in the pattern of remodelling seen in IPF. Farkas et al reported vessels with isolated medial hyperplasia, vessels with intimal lesions, vessels obstructed with scar tissue and plexiform lesions (Farkas

et al., 2009). Furthermore, it appears that the extent of these changes correlates with the disease activity in surrounding areas (Farkas et al., 2009).

1.2.4.5 Pathophysiology of PH in Sarcoidosis

Additional factors are also important in the development of PH in Sarcoidosis (Nunes et al., 2006). Enlarged mediastinal lymphadenopathy can compress pulmonary arteries. Cardiac sarcoidosis can result in left ventricular systolic or diastolic dysfunction. The pulmonary arteries can be directly infiltrated by granulomatous inflammation as can the pulmonary venous system resulting in pulmonary veno-occlusive disease (Hoffstein et al., 1986).

1.3 Interstitial Lung Disease associated PH

1.3.1 Prevalence of ILD-PH

It is difficult to accurately assess the prevalence of PH occurring in ILD, and prevalence is strongly determined by the specific subtype of ILD studied in addition to the screening method used. RHC is the gold standard, although often studies evaluating the prevalence of ILD rely on echocardiography despite its inaccuracies (Nathan et al., 2008b, Arcasoy et al., 2003). Selection bias is an important determinant of PH prevalence in ILD patients, where PH appears more prevalent due to the population studied and inclusion criteria. Where 246 consecutive Japanese patients with biopsy confirmed sarcoidosis were screened with echocardiography (PH defined as a right ventricular systolic pressure (RVSP) ≥40mmHg), just 5.6% had PH (Handa et al., 2006). Whereas in a sarcoidosis cohort with chronic exertional dyspnoea, 47% of 53 patients had PH (mPAP ≥25mmHg at RHC) (Baughman et al., 2010). PH becomes more prevalent as the underlying ILD progresses illustrated by longitudinal RHC analysis in a transplant population with IPF, with the prevalence of PH increasing from 38%

at initial evaluation RHC to 78% of the cohort at the time of the transplant (Nathan et al., 2008a). However, in mild to moderate IPF (where RHC was performed prospectively; the ARTEMIS study, a placebo-controlled trial of the endothelin receptor antagonist, ambrisentan). 1087 patients were screened. Important exclusion criteria were a functional class (FC) of III or more, co-existent airflow obstruction at spirometry or emphysema at CT, and a left ventricular (LV) ejection fraction of <40%. 488 patients underwent RHC assessment. 68 (14%) had group 3 PH, 25 (5%) had group 2 PH, a further 21 (4%) had an elevated PCWP but not PH and 374 (77%) did not have PH. (Raghu et al., 2013a). In addition to the 14% with PH at baseline another 30% of the cohort had mPAP in the so called "grey zone" of ≥20 and <25mmHg. Despite stringent exclusion criteria (FC II or less and <5% honeycombing on CT) a high proportion of patients had PH at RHC and nearly another third of the cohort had borderline PH.

The prevalence of PH in ILD other than IPF is much less well understood, with no prospective studies with RHC to inform of ILD prevalence at presentation. All studies quoted in table 1.3 below (outside of IPF), were either performed in pre-transplant populations or in patients who had a high pre-test probability of PH, therefore strongly influencing the likelihood of PH. Estimating the prevalence of PH in CTD is extremely difficult as PH can occur both in isolation and together with ILD. In SScl isolated pulmonary hypertension is more common in patients with limited SScl, whereas ILD is more common in diffuse SScl (Steen et al., 1985). PH and ILD is strongly linked to antibody status with PH being more common in anti-centromere positivity, whereas ILD is more common in anti-topoisomerase positivity (Nihtyanova et al., 2014). The only study which evaluated the prevalence of PH in SScl both

with and without interstitial lung disease used echocardiography as the screening tool in patients with various stages of disease (B Chang, 2003). Of 619 patients, 139 (22.5%) had isolated restrictive lung disease, 119 (19.2%) had isolated PH (defined as RVSP ≥35mmHg), and 112 (18.1% had both restrictive lung disease and PH at echo) (B Chang, 2003). Patients with more severe restrictive lung disease were more likely to have PH (51.4% versus 39.2% with mild restriction). Studies evaluating the prevalence of PH occurring in ILD are summarised in table 1.4.

ILD	ILD severity	Number of patients	Diagnostic modality	Threshold (mmHg)	PH prevalence (%)	Author / reference
IPF	Early	61	RHC	≥25	8.1	(Hamada et al., 2007)
IPF	Early	101	RHC	≥25	14.9	(Kimura et al., 2013)
IPF	Early	492	RHC	≥25	14	(Raghu et al., 2013a)
IPF	Pre-Tx	79	RHC	≥25	31.6	(Lettieri et al., 2006)
IPF	Pre-Tx	2525	RHC	≥25	46.1	(Shorr et al., 2007)
IPF	Pre-Tx	58	RHC	≥25	43	(Modrykamien et al., 2010)
PM/DM	Early	61	Echo	≥40	16.4	(Wang et al., 2015)
Antisynthetase	Mixed	203	Echo		23.2	(Hervier et al., 2013)
Sarcoidosis	Mixed	212	Echo	≥40	5.7	(Handa et al., 2006)
Sarcoidosis	Mixed	162	RHC	≥25	13	(Bourbonnais and Samavati, 2008)
Sarcoidosis	Persistent dyspnoea	130	RHC	≥25	54	(Baughman et al., 2010)
Sarcoidosis	Pre-Tx	25	RHC	≥25	79	(Milman et al., 2008)
Sarcoidosis	Pre-Tx	363	RHC	≥25	73.8	(Shorr et al., 2005)
Chronic HP	Mixed	50	RHC	≥25	50	(Oliveira et al., 2014)
Langerhans	Pre-Tx	39	RHC	≥25	92	(Dauriat et al., 2006)
Mixed ILD	Mixed	212	RHC	≥25	14	(Andersen et al., 2012)

Table 1.4. Prevalence of PH in different ILDs and different severities of ILD

Abbreviations: IPF - Idiopathic pulmonary fibrosis, PM - Polymyositis, DM - Dermatomyositis, HP - Hypersensitivity pneumonitis, Pre-Tx - pre-transplant, RHC - Right heart catheter, Echo - echocardiography

1.3.2 Prognostic significance of ILD-PH

In general studies evaluating prognosis in ILD-PH have been performed within the same studies evaluating both prevalence and prediction of ILD-PH. Therefore, selection bias which heavily influences prevalence of PH in ILD is also likely to affect prognostic analysis. It is likely that factors which predict mortality in early and late disease change as the disease progresses. Table 1.5 shows the invasive and non-invasive variables which have been associated with increased mortality in ILD-PH at baseline analysis. Only one study has performed a longitudinal analysis evaluating mortality in patients with SScl associated ILD-PH and found that worsening hypoxia and reduced renal function were the only significant predictor of mortality at longitudinal analysis (Le Pavec et al., 2011).

ILD	Number of patients	Variable predicting mortality	Hazard Ratio	Relative Risk	P-value / confidence interval	Author
	Haemodynamic					
Mixed	212	PH at RHC (≥25mmHg)	8.5	-	<0.001	(Andersen et al., 2012)
Sarcoid	130	PH at RHC (≥25mmHg)	10.4	-	<0.001	(Baughman et al., 2010)
IPF	61	mPAP >17mmHg	-	2.2	<0.001	(Hamada et al., 2007)
IPF	79	mPAP (per 1mmHg increase)	1.09	-	1.02-1.16	(Lettieri et al., 2006)
IPF	101	mPAP (per 1mmHg increase)	1.08	-	0.001	(Kimura et al., 2013)
IPF	135	PVR per one Wood unit increase	1.3	-	1.1-1.5	(Rivera-Lebron et al., 2013)
Mixed	66	PVR >6.3 Wood units	8.2	-	0.001	(Corte et al., 2009)
		PH at RHC (≥25mmHg)	3.00	-	0.18	
	Echocardiography					
IPF	135	RV:LV ratio >1.0	3.8	-	0.006	(Rivera-Lebron et al., 2013)
		RA dilatation	2.4	-	0.009	
		RV dilatation	2.6	-	0.001	
		RV dysfunction	4.9	-	<0.001	
Mixed ≠	133	PVR*echo* >2.05	3.65	-	0.02	(Yasui et al., 2016)
IPF ≠	136	RVSP (Per 10mmHg increase)	-	1.34	<0.001	(Nadrous et al., 2005)
	Brain natriuretic peptide					
Mixed	176	BNP ratio >1.0	-	2.94	<0.01	(Leuchte et al., 2006)
IPF ≠	131	Elevated BNP ratio	10.3	-	<0.001	(Song et al., 2009)
Mixed ≠	90	BNP (x5 limit of normal)	2.93	-	0.01	(Corte et al., 2010b)
	Pulmonary function tests					
IPF	61	TLco < 40% predicted		2.5	<0.001	(Hamada et al., 2007)
IPF	135	FVC (per 1% increase)	0.96	-	<0.001	(Kimura et al., 2013)

Table 1.5. Invasive and non-invasive variables which independently predict mortality in ILD-PH

Abbreviations: IPF - Idiopathic pulmonary fibrosis, PH - Pulmonary hypertension, RHC - Right heart catheter, mPAP - Mean pulmonary pressure at RHC, PVR - Pulmonary vascular resistance, RV - Right ventricle, LV - Left ventricle, RA - Right atrium, RVSP - Right ventricular systolic pressure, BNP - Brain natriuretic peptide, TLco - Transfer factor. ≠ These studies were performed without PH being confirmed at RHC.

1.3.2.1 Prognostication with haemodynamics

mPAP has been found to be an independent predictor of mortality in both early and later stage ILD (Andersen et al., 2012) (Baughman et al., 2010) (Hamada et al., 2007) (Lettieri et al., 2006) (Kimura et al., 2013). However in other studies in IPF patients undergoing RHC, mortality was most strongly linked to increases in PVR whereas mPAP did not predict mortality (Rivera-Lebron et al., 2013). These observations were mirrored in a cohort of ILD patients: early mortality was strongly linked to a marked increase in PVR (Corte et al., 2009).

1.3.2.2 Prognostication with echocardiography

In 135 patients with IPF referred for lung transplant who underwent both echocardiography and RHC, the RV:LV ratio, moderate to severe RA dilation, moderate to severe RV dilation, moderate to severe RV dysfunction and RVSP (per 5mmHg increase) all predicted mortality (Rivera-Lebron et al., 2013). In a small study in 17 patients with pulmonary Langerhan's cell histiocytosis the development of PH at echo (RVSP >35mmHg) was associated with mortality (HR:22.8, CI:7.6-68.9, $p<0.001$) (Chaowalit et al., 2004a). In a mixed ILD cohort PVR calculated by echocardiography predicted mortality (Yasui et al., 2016). In an IPF population, median survival was 4.7 years and 4.1 years in patients with RVSP of 0-34mmHg and 35-49mmHg respectively but was only 0.7 years in patients with RVSP>50mmHg (Nadrous et al., 2005).

1.3.2.3 Prognostication with brain natriuretic peptide

The prognostic significance of elevated brain natriuretic peptide (BNP) levels was first explored in 176 patients with a mixture of chronic pulmonary diseases including ILDs of various sub-types (Leuchte et al., 2006). Severe PH (mPAP >35mm Hg) was present in 25% of cases and increasing BNP levels were a risk factor for mortality. In a cohort of 90 patients

with a mixture of ILDs, higher BNP concentrations were associated with increased mortality (Corte et al., 2010b). In this study, patients with BNP ≥ 20pmol/L had a 14-fold increase in mortality over patients with BNP < 4 pmol/L. In a review of 131 IPF patients undergoing echocardiography and BNP measurement, increased BNP levels were predictive of mortality with no added prognostic value provided by echocardiographic data (Song et al., 2009).

1.3.2.4 Prognostication with pulmonary function tests

A moderately to severely reduced gas transfer (TLco) of <40% predicted was independently predictive of mortality (Hamada et al., 2007) in 70 IPF patients who underwent RHC prospectively. In a fibrotic IIP study, gas transfer adjusted for alveolar volume (Kco), was associated with increased early and overall mortality (Corte et al., 2012a). In two fibrotic IIP series, a six-month decline in Kco was predictive of increased mortality, (Corte et al., 2012a, Peelen et al., 2010) and was associated with an increased likelihood of the development of echocardiographic evidence of PH (Corte et al., 2012a).

1.3.2.5 Prognostication with main pulmonary artery diameter and main pulmonary artery to aorta ratio

Main pulmonary artery diameter (MPAD) appears to be important in risk stratification in patients with chronic respiratory disease. In chronic obstructive pulmonary disease (COPD) an increase in the MPAD to aorta diameter ratio (MPAD:Ao) is associated with a higher risk of future exacerbation (Wells et al., 2012) and mortality (Shin et al., 2014). In IPF the MPAD has been shown to increase in diameter during an acute exacerbation relative to baseline MPAD diameter, although its relationship to mortality and other pulmonary vascular markers was not explored further. Recently an increase in MPAD:Ao ratio has been shown to be an independent predictor of mortality in 98 patients with IPF (Shin et al., 2016).

1.3.3 Diagnosis of ILD-PH

At present RHC is the gold standard reference for diagnosing PH in ILD patients. The threshold for diagnosing PH has been extrapolated from PAH experience. The first official haemodynamic definition of primary PH was in the first World Symposium in Geneva in 1973 and was defined as a mPAP ≥25mmHg at RHC or a mPAP ≥30mmHg during exercise with a PCWP ≤15mmHg. The threshold mPAP ≥25mmHg was evaluated in a systematic review of 47 studies in 1,187 healthy patients (Kovacs et al., 2009). mPAP was 14.0±3.3mmHg, and increased variability was found in mPAP during exercise such that exercise evaluation of mPAP is no longer recommended. The extrapolation of the same mPAP (to diagnose PH) may not accurately predict risk in patients with ILD. A prospective study evaluating 61 patients (who had RHC as part of their initial workup), found that 5-year survival rates were 62.2% (n=37) in patients with a mPAP <17mmHg, and 16.7% (n=24) in patients with a mPAP >17mmHg ($p<0.01$) (Hamada et al., 2007). Another study where RHC was performed at initial workup had similar findings with a mPAP of >20mmHg to be the best threshold to predict of mortality (Kimura et al., 2013). These studies suggest that in early IPF modest elevation in mPAP are important and may identify individuals who are rapid progressors or are at an increased risk of mortality.

1.3.3.1 Diagnosis of PH using Echocardiography

According to European society of Cardiology and Respiratory (ESC/ERS) guidelines, estimation of PH by echocardiography should be based upon assessment of peak tricuspid regurgitation velocity (TRv) in addition to 'additional echocardiographic PH signs' (Galie et al., 2016). Studies have evaluated the ability of the RVSP to predict the presence of

pulmonary hypertension which is calculated thus: RVSP = 4 x Tricuspid regurgitation valve maximum² + right atrial pressure. For example, Arcasoy et al demonstrated that RVSP estimation was only possible in 44% of 374 patients with advanced lung disease (28% of which had ILD). 25% with measurable RVSP were considered to have echocardiographic PH (RVSP >45mmHg). At RHC, it transpired that the diagnosis of PH was falsely positive in 48% and that, echocardiography over-estimated RVSP by approximately 10mmHg, although underestimation also occurred in a minority. This resulted in 48% of patients being misclassified as having PH (Arcasoy et al., 2003). Another significant difficulty with screening tests remains the choice of threshold. Nathan et al (2008) evaluated 110 IPF patients, where TRv was seen in 54.5% of the cohort, (PH occurred in 32% of the individuals where no TRv was measurable). Depending upon the RVSP threshold used, positive predictive values for PH vary between 35% and 65% (46% if RVSP >50 mmHg) with negative predictive values ranging from 65-80%. An adequate threshold RVSP to predict PH could not be demonstrated. The high false positive rate indicates that echocardiographic PH is more likely to represent a true positive when the pre-test likelihood is high (Nathan et al., 2008b). A recent echocardiographic study also evaluated RHC measurements in 192 patients with advanced lung disease, (54% of whom had ILD), where RVSP could be measured in only 52% of the cohort (Amsallem et al., 2017). The authors concluded that where a good tricuspid regurgitation envelope was available, RVSP did reliably detect PH. Although, with TRv present, the integration of other right heart abnormalities did *not* add to the prediction of PH. However, 47% of patients without a measurable RVSP had PH, and the presence of two

or more abnormal right heart measures did discriminate between patients with and without PH, especially when PH was severe (defined as mPAP ≥35mmHg) (Amsallem et al., 2017).

1.3.3.2 Diagnosis of PH using pulmonary function tests

In IPF, most pulmonary function variables are similar comparing patients with and without PH (Lettieri et al., 2006). Gas transfer (TLco) levels are strongly influenced by both pulmonary vascular disease and the severity of ILD, and so are an unreliable screening tool. In one IPF cohort, PH was more frequently present when the TLco level was < 30% and FVC was >70% predicted (Nathan et al., 2007). In SScl, an increased FVC/TLco ratio has been shown to be associated with an increased likelihood of PH, including when ILD was clinically present (Steen et al., 2008, Hsu et al., 2008, Launay et al., 2011). The DETECT study is an externally validated tool to screen SScl patients for PH, which employs the FVC/TLco ratio, although only a minority of the study group had clinically relevant ILD. (Coghlan et al., 2014). It is likely that Kco and the FVC/TLco ratios ability to discern PH is confounded in emphysema resulting in reduction in TLco and falsely increase / preserve the FVC (Antoniou et al., 2016).

In a cohort with advanced interstitial lung disease of various types, the 6MWD was significantly reduced, and oxygen desaturation was greater, in patients with PH at RHC (Kawut et al., 2005). Prolonged heart rate recovering following a six-minute walk test was predictive of the presence of PH at right heart study in an IPF cohort of 160 patients (Swigris et al., 2011). A prolonged heart rate recovery had a sensitivity, specificity, positive predictive value and negative predictive value of 52%, 74%, 41% and 82% respectively for the prediction of PH.

1.3.3.3 Diagnosis of PH using brain natriuretic peptides

In an early PH diagnostic study of BNP in a mixed ILD cohort of 39 patients BNP levels correlated strongly with mPAP ($r=0.74$, $p<0.001$), and PVR ($r=0.8$,$p<0.001$) (Leuchte et al., 2004). When BNP was increased, six-minute walk distance and cardiac output were both reduced. A BNP threshold of 33pg/ml had a receiver operator curve (ROC) area under the curve of 96% in identifying severe PH (mPAP>35mm) (Leuchte et al., 2004). Serum BNP may be most helpful when levels are normal and, well below thresholds generally associated with PH. This is supported in a recent mixed ILD cohort of 118 patients, where having a "normal" NT-proBNP (<95 ng/l) at initial diagnostic evaluation precluded an echocardiographic finding of an RVSP of ≥40mmHg (Andersen et al., 2016).

1.3.3.4 Diagnosis of PH using main pulmonary artery diameter measured at CT

HRCT is a cornerstone of ILD diagnosis and repeat imaging is often performed following an interval or following a deterioration in symptoms or PFT. The MPAD or MPAD:Ao could act as a barometer for the pulmonary vasculature, and indicate when patients should undergo evaluation for PH. Initial studies in lung transplant candidates were good (Tan et al., 1998) where a retrospective study found a threshold for the MPAD of ≥29mm predicted PH at RHC with a sensitivity of 84% and specificity of 75% although there was no correlation between the MPAD and mPAP at RHC. Future studies (Devaraj et al., 2008, Zisman et al., 2007a), and a prospective study in 134 patients where CT and RHC were performed within 72 hours of each other (Alhamad et al., 2011) showed that MPAD and MPAD:AA were unreliable in predicting PH, in the presence of ILD. In these studies, MPAD occurred in the absence of PH at right heart catheter. It was suggested that parenchymal fibrosis increases intra-thoracic pressure which pulls apart the main pulmonary artery rather than being internally dilated by

increased pressure from within the pulmonary artery (Ng et al., 1999, Zisman et al., 2007a). A further study in 48 Scleroderma associated ILD patients supported this and showed that where forced vital capacity (FVC) was > 70% predicted the correlation of MPAD and mPAP was strong and where FVC was <70% predicted no correlation was seen (McCall et al., 2014). However, recently a study in 110 patients with ILD found that the MPAD measured at CT was accurate for detection of PH with an area under the curve of 0.84. Furthermore, significant correlation was seen between MPAD and mPAP measured at RHC, and ILD severity was not associated with MPAD dilatation (Chin et al., 2018). A further recent study has shown that a diagnostic CTPA model made up of MPAD, RV outflow tract thickness, septal angle and LV area was diagnostic of PH at RHC (AUC 0.94) {Swift, 2020 #513}. The same model also predicted mortality. These recent studies show us the diagnostic and prognostic utility of imaging in patients with suspected PH.

1.3.4 Treatment of ILD-PH

Unfortunately, at present there is no specific therapy approved for PH associated with IIP, and the evaluation of pulmonary vasodilators in IIP-PH has so far failed to show benefit, and some appear to cause harm. The 5th World Symposium of Pulmonary Hypertension and the European Society of Cardiology / European Respiratory Society PH guidelines (Galiè et al., 2015), and the ATS/ERS guideline do not advocate the routine use of pulmonary vasodilators (Raghu et al., 2015) in IIP-PH, but suggest further clinical trials before recommendations can be made. Both advocate optimization of the underlying disease process and oxygen therapy. Given ILD occurs in patients with several co-morbidities factors which propagate the development of PH should be sought and addressed.

1.3.4.1 Hypoxia

The landmark oxygen studies conducted in patients with COPD in the early 1980's (Council, 1981, Group, 1980) have been extrapolated to formulate recommendations for oxygen therapy in many chronic respiratory conditions such as ILD and PH (Society, 2015). Without any more specific, or more recent studies these recommendations apply to patients with ILD and PH.

1.3.4.2 Sleep disordered breathing

Nocturnal desaturation is very common in ILD with most prospective studies being performed in IPF; the incidence of obstructive sleep apnoea (OSA) varying from 59 to 90% (Kolilekas et al., 2013, Pihtili et al., 2013, Mermigkis et al., 2010). Nocturnal desaturation can occur even in the absence of OSA (Perez-Padilla et al., 1985). Patients who are hypoxaemic during the day show more severe nocturnal desaturation (Midgren et al., 1987, Clark et al., 2001, Midgren, 1990). Disproportionate nocturnal desaturation has been found in patients with mild ILD and correlated with signs of PH on echocardiogram (Corte et al., 2012b), as well as being an independent predictor of prognosis (Kolilekas et al., 2013, Corte et al., 2012b).

1.3.4.3 Thrombosis

Large epidemiological studies have suggested an association between IPF and vascular thrombotic diseases (Hubbard et al., 2008, Sode et al., 2010, Sprunger et al., 2012). A recent large-scale epidemiological study analysing mortality data demonstrated a 34% higher risk of a venous thromboembolism (VTE) in IPF patients above the background population (Sprunger et al., 2012). A small prospective trial performed baseline CT pulmonary angiograms (CTPA) and a follow up CTPA at three months in IIP patients who

showed no symptoms or signs of having had a pulmonary embolus (PE). One third of the patients had evidence of PE on either their baseline or follow up CTPA (Luo et al., 2014).

1.3.4.4 Prevention and treatment of exacerbations

Acute exacerbation in (best reported and studied in IPF) represents a period of rapid worsening of symptoms and decline in pulmonary function, and is the most common cause of deterioration and death in IPF (Kim et al., 2006, Song et al., 2011). IPF patients with PH have been shown to be at a higher risk of future exacerbations (Judge et al., 2012). The cause of an acute exacerbation often is not clear although infection (Huie et al., 2010), is nearly always suspected. Although an association with air pollution (Johannson et al., 2014) and micro-aspiration (Lee et al., 2012) has also been demonstrated. Unfortunately, no proven treatment has been shown to improve the prognosis in acute exacerbation therefore supportive measures such as oxygen therapy, broad-spectrum antibiotic therapy and careful control of fluid balance are recommended.

1.3.4.5 Evidence for the use of pulmonary vasodilators

1.3.4.5.1 Phosphodiesterase type-5 inhibitors (PDE-5)

Sildenafil has predominantly been evaluated in non-randomised, open label populations with proven ILD-PH. The first open label trial (16 patients, 7 with IPF) compared the vasodilatory effects of oral sildenafil and IV prostacyclin after nebulised NO (10-20ppm). PVR fell by 32.5% PVR (CI: -10.2 to -54.1), with no change in ventilation and perfusion matching (oxygen saturations increased). However use of IV prostacyclin resulted in increased ventilation and perfusion mismatching which worsened hypoxaemia (Ghofrani et al., 2002). Another small open label trial evaluated the effect of sildenafil on 6MWD which

included 14 patients with IPF associated PH. More than half of the 11 patients who completed screening (57%) improved their 6MWD by > 20%. Sildenafil use (over a median follow up of 91 days) was well tolerated (Harold R. Collard, 2007). Thirdly, a small retrospective case-series was performed in 15 patients with ILD and PH confirmed by RHC or echocardiography. Following 6 months of sildenafil serum BNP and 6MWD improved although there was no change in RVSP at echo, arterial oxygen saturation or pulmonary function tests variables (Corte et al., 2010a). Finally, a small observational pilot study (10 patients, 6 with IPF) evaluated haemodynamics in an open label study of PDE-5 inhibitors sildenafil or tadalafil. Cardiac index increased significantly and PVR fell. Mean PAP was shown to fall but did not quite achieve statistical significance. No improvement was seen in 6MWD, BNP or PFT (Zimmermann et al., 2014).

The largest experience of oral sildenafil in ILD is the double-blind, randomised, placebo-controlled study STEP-IPF study. Although PH was not confirmed at RHC the inclusion criterion (TLco <35%) made it likely that a high proportion of patients will have had PH. The primary outcome was a 20% improvement in 6MWD, which was not met. However, several secondary outcome measures were met including an improvement in TLco, partial pressure of oxygen and, QOL scores improved. The improvement in TLco and oxygen saturations suggests that sildenafil was directly affecting the pulmonary vasculature (Zisman et al., 2010). Pre-enrolment echo evaluation was possible in 119 of 180 patients, the effect of sildenafil in patients with right ventricular dysfunction (RVSD) was evaluated. Patients on sildenafil with RVSD experienced a lesser drop (99.3m p = 0.01) in 6MWD than patients with RVSD who were on placebo (Han et al., 2013). (The minimal clinical important difference for

6MWD in IPF was evaluated by (du Bois et al., 2011c) and found to be 24-45m. QOL scores (St Georges Respiratory Questionnaire) also improved in patients on sildenafil (Han et al., 2013).

Another more recent retrospective study (using an international registry COMPERA) evaluated patients with IIP and compared them with idiopathic pulmonary arterial Hypertension (IPAH) patients. There were 151 incident IIP patients, who were significantly older than the IPAH patients. 95% of the IIP-PH patients were treated with single pulmonary vasodilator therapy, 88% of which was a PDE5i. Treatment was associated with a 24.5m improvement in 6MWD in IIP-PH and 30m in IPAH patients. FC improved in 22.4% in IIP-PH and 29.5% of IPAH. Patients who improved their 6MWD by at least 20m or improved FC had a better prognosis than patients who did not respond (Hoeper et al., 2015).

A retrospective study in 24 patients with sarcoidosis found that treatment with sildenafil for 4 months was associated with a reduction in mPAP by -8mmHg (CI: -1 to -15mmHg, p=0.03), and PVR by -4.9 Wood units (-2.6 to -7.2 Wood units, p<0.001). Cardiac output and cardiac index also increased with treatment (p=0.01) although there was no significant increase in the 6MWD (Milman et al., 2008).

1.3.4.5.2 Endothelin receptor antagonists

As well as its role constricting pulmonary vessels ET-1 is also profibrotic (Ross et al., 2010), and elevated levels have been demonstrated in patients with IIP (Uguccioni et al., 1995, Trakada and Spiropoulos, 2001). Levels correlate with pulmonary arterial pressure and in a negative trend with arterial oxygen levels in a small group of ILD patients (Trakada and

Spiropoulos, 2001). ET-1 was therefore targeted to try and attenuate both the fibrotic progression and to try and the development of pulmonary vascular disease.

BUIILD-3 was a large randomized placebo controlled trial which showed bosentan to be safe and well tolerated in IPF although no difference was demonstrated time to worsen clinically or death (hazard ratio, 0.85 95% CI, 0.66-1.10) (King et al., 2011). Another study (MUSIC) evaluated 178 patients with biopsy proven IPF (FVC > 50% predicted and TLCO > 30%) in a prospective randomised double-blind placebo-controlled study with macitentan. There was no difference seen in FVC at 12 month follow up or any other of the secondary outcomes (Raghu et al., 2013c). Artemis-IPF was a randomized double-blind placebo-controlled trial evaluating the ambrisentan in IPF and IPF-PH. Interim analysis showed ambrisentan treated patients were more likely to experience the primary outcome of disease progression than patients on placebo, the trial was therefore terminated. Sub-analysis of the 10% with PH demonstrated no difference although the study was not powered in this subgroup (Raghu et al., 2013b). Bosentan in Pulmonary Hypertension associated fibrotic idiopathic interstitial pneumonia (B-PHIT) was the first randomised, double blind placebo-controlled study evaluating PH specific treatment in IIP-PH. The study failed to show any improvement in invasive haemodynamics, FC, 6MWD, or QOL scores, and subgroup analysis could not demonstrate a group that benefited (Corte et al., 2014).

Bosentan has been evaluated in a small 16-week double-blind placebo controlled randomised trial in sarcoidosis (Baughman et al., 2014). 35 patients completed 16 weeks of therapy. Treatment with bosentan resulted in a fall in mPAP -4±6.6mmHg (p=0.01), and PVR -1.7±2.75 Wood units (p=0.01), whereas placebo was associated with no change. There was

no increase in 6MWD, and 2 patients treated with bosentan required up-titration of their oxygen therapy after 16 weeks of therapy (Baughman et al., 2014). Ambrisentan has also been evaluated in a small open label proof of concept study in 21 subjects with sarcoidosis (Judson et al., 2011). Although only 10 (48%) could complete the study. FC improved and QOL improved although did not reach statistical significance thought to be due to the large dropout rate. The cause of patient withdrawal was dyspnoea in 6/21 (29%) and/or oedema 4/21 (19%). Ambrisentan seemed to be poorly tolerated in this sarcoidosis cohort (Judson et al., 2011).

1.3.4.5.3 Prostanoids

Studies on prostanoids have been small, non-randomised, and focused on invasive haemodynamics. In one study with 8 ILD patients with severe underlying pulmonary fibrosis, inhaled iloprost caused pulmonary vasodilatation with maintenance of gas exchange and systemic arterial pressure. Whereas iv prostacyclin resulted in a significant drop in systemic arterial pressure and a marked worsening in V/Q mismatching (Olschewski et al., 1999).

Nebulised iloprost has been evaluated in an open label prospective study in 22 sarcoid patients, 15 of which completed 16 weeks of therapy (Baughman et al., 2009). Although haemodynamics did not improve sufficiently to reach statistical significance there was a statistical improvement in QOL (Baughman et al., 2009). A retrospective study evaluated 8 patients with fibrotic sarcoidosis, with mild to moderate PH. Seven patients were treated with IV epoprostenol, and 6 of the 7 patients had a >25% reduction in PVR, and functional class improved one to two WHO functional classes (Fisher et al., 2006).

1.3.4.5.4 Guanylate cyclase stimulators

Riociguat is a soluble guanylate cyclase stimulator that can synergise with endogenous NO and can act independently of NO. It has been shown to improve 6MWD and haemodynamics in PAH (Ghofrani et al., 2013). In a pilot study (open-label, non-blinded, non-randomised) to assess safety and tolerability in patients with mild to moderate ILD but moderate to severe PH (n = 23, 82% of patients had underlying IIP), riociguat was well tolerated. PVR decreased, and cardiac output increased, with mPAP remaining unchanged (Hoeper et al., 2013). Therefore a, double blind placebo controlled trial on efficacy and safety of riociguat in IIP-PH (RISE-IIP) was commenced in 2014 (Bayer, NCT02138825.). This study has recently been stopped prematurely due to increased mortality in the treatment arm. Bayer has recommended that riociguat is not used in IIP patients.

A summary of all vasodilator studies in ILD is shown in table 1.6. It is very frustrating that all studies have shown a lack of benefit and some have shown harm. However, there is a signal that PDE-5 inhibitors appear to be well tolerated and may be associated with benefit. What is not clear is which group of patients with IIP will benefit, and at what stage of disease therapies may benefit patients. Most studies have been performed in IIP patients who have advanced disease. It is possible that commencing vasodilators prior to the onset of RVD / established PH offer more benefit than waiting until PH is established.

ILD	Treatment	Duration (months)	Number of patients	Primary end-point	Study result	Type of study	Target	Author / reference
IPF	Bosentan	12	154	6MWD	No change	R,D,P	IPF	(King et al., 2008)
IPF	Bosentan	12	616	Disease progression	No change	R,D,P	IPF	(King et al., 2011)]
IIP	Bosentan	4	60	↓PVR	No change	R,D,P	IIP-PH	(Corte et al., 2014)
Sarcoid	Bosentan	4	35	↓PVR	↓PVR	R,D,P	SAPH	(Baughman et al., 2014)
IPF	Ambrisentan	9	492	Disease progression	Negative	R,D,P	IPF	(Raghu et al., 2013b)
IPF	Macitentan	12	178	FVC	No change	R,D,P	IPF	(Raghu et al., 2013c)
IPF	Sildenafil	3	180	6MWD	No change	R,D,P	IPF	(Zisman et al., 2010)
IPF	Sildenafil	3	119	6MWD	Preservation of 6MWD	R,D,P Sub	IPF (RVSD)	(Han et al., 2013)
Mixed	Sildenafil / Tadalafil	3	10	-	↓ PVR, ↑ CI	Open	ILD-PH	(Zimmermann et al., 2014)
Mixed	Riociguat	12	15	Safety	No Safety concerns	Open	ILD-PH	(Hoeper et al., 2013)
IIP	Riociguat	6.5	147	6MWD	Negative	R,D,P	IIP-PH	(Bayer, NCT02138825.)

Table 1.6. Studies evaluating vasodilators in patients with IIP and ILD-PH

Abbreviations: 6MWD - six-minute walk distance, FVC - change in FVC, PVR - pulmonary vascular resistance, RVD - right ventricular dysfunction on echo, CI - cardiac index, R - randomized, D - double blind, P - placebo controlled, Open - Open label, Sub - sub study analysis

1.5 Hypothesis

I hypothesized that It is possible to predict the presence of pulmonary hypertension using non-invasive variables, and that prognosis can be predicted using baseline and longitudinal change in non-invasive variables.

1.6 Aims

1. To develop an algorithm using non-invasive variables to predict if a patient with ILD has developed ILD-PH.
2. To evaluate novel CT pulmonary angiography-based markers ability to predict and prognosticate in suspected ILD-PH.
3. To evaluate the ability of non-invasive markers of ILD and PH severity in predicting prognosis at the time of diagnosis of ILD associated PH.
4. To evaluate if longitudinal change in non-invasive markers in ILD-PH predict prognosis.

CHAPTER 2: Methods, and defining the ILD-PH Cohort

2.1 General introduction

The PH Service at the Royal Brompton and Harefield Hospitals (RBH) NHS Foundation Trust forms part of the National Pulmonary Hypertension Service and is one of six designated PH centres in England & Wales. The clinical service provides advice for patients and staff, diagnostic investigation, treatment, and long term follow up of patients with PH who come mainly from the south of England and Wales.

The ILD unit at RBH is the largest unit of its kind in Europe. The unit plays a central role in re-classification of ILDs and frequently contributes expert opinion on pathogenesis, clinical manifestations, treatment, radiology and histopathology to the American Thoracic and European Societies. The ILD unit and PH service have a long history of working together and have performed the only placebo controlled double blind study of advanced PH therapies in ILD-PH (Corte et al., 2014).

2.2 Defining the cohort

Consecutive patients with ILD referred to our National Pulmonary Hypertension Service with suspected PH between 2005 and 2015 were reviewed. This study had institutional review board approval (Royal Brompton, Harefield reference 2016PH002B).

As part of its role, the national PH service has collected data for the National Pulmonary Hypertension Audit (NPHA) database, and it is from this data set that historical ILD-PH patients were located. Mandatory data for all PH patients includes a range of clinical data

including demographics, date of investigations including: RHC, six-minute walk tests, WHO functional status, PH-specific quality of life data and treatment status. Retrospective analysis of this database enabled identification of all patients diagnosed with PH and the clinical class of their PH diagnosis. By cross-referencing with the historical RHC database and clinical records it was possible to identify patients who underwent RHC with suspected ILD-PH. Any patient having their first RHC between 2005 and September 2015 was analysed for eligibility to be recruited into the ILD-PH cohort.

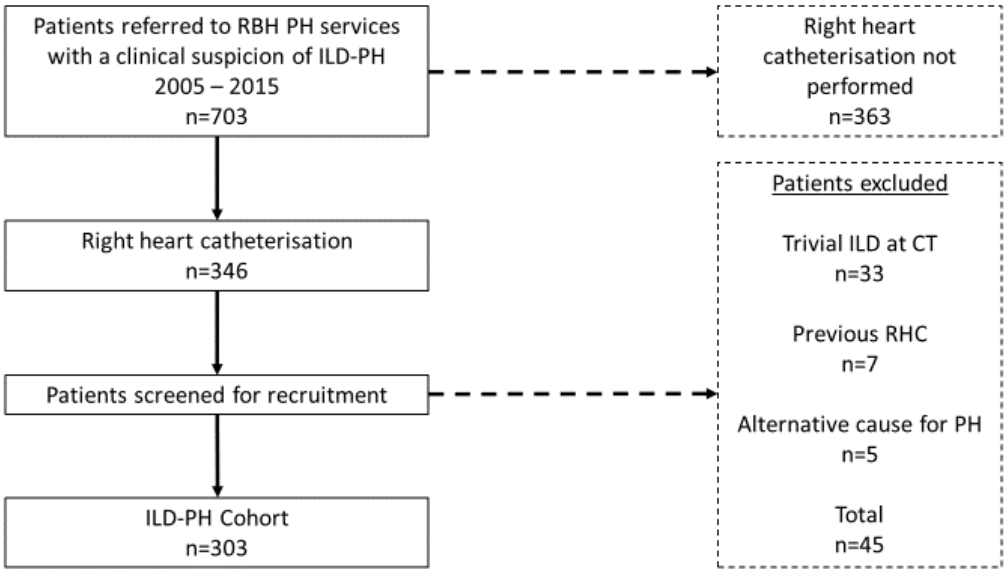


Figure 2.1. Flowchart demonstrating patient identification and exclusion

Abbreviations: RBH - Royal Brompton Hospital, ILD - interstitial lung disease, PH - pulmonary hypertension

2.2.1 ILD Subtypes recruited

PH in ILD has been reported in virtually all ILD diagnoses and to improve recruitment to the study all ILD diagnoses were eligible. One of the inclusion criteria for the study group was

ILD extent at CT which excludes any patient with no or minor ILD. This grouping of all the ILD patients is an accepted methodology and can be compared to the grouping of "group 1 / PAH" patients; where, despite variation in clinical outcome within the group there are similarities in pathophysiology and disease course.

2.2.2 Inclusion criteria for incorporation into the cohort as a whole

- Age > 18 years of age.
- Right heart catheterisation performed.
- A diagnosed Interstitial lung disease (to include unclassifiable ILD).
- ILD severity derived from CT > 5% total extent.

2.2.3 Exclusion criteria

- Diagnosis with an additional cause for PH following workup and MDT discussion.
- Prior RHC demonstrating PH.
- If multiple RHC were performed within the study period, then the patient was recruited from the date of the RHC which confirmed PH.
- Lack of CT scan of adequate diagnostic quality for ILD severity assessment.
- No or minor ILD at HRCT severity assessment.

2.3 Measured and recorded variables

All baseline non-invasive investigations at RHC were collected. A 6-month interval prior to and after the RHC was used for collection of baseline values. If multiple tests were performed within the interval then the investigation closest to the RHC was used, with preference given to tests performed prior to RHC.

2.3.1 Right heart catheterisation

Patients were electively admitted for a planned admission, all patients were nill by mouth on the morning of the procedure. Care was taken with all patients to postpone RHC unitl a period where the patient was clinically stable and free from recent exacerbation. RHC was performed using standard techniques (Galie et al., 2016) with haemodynamic measurements obtained at rest in all patients. PH was defined as a mean pulmonary arterial pressure (mPAP) ≥25mmHg, and severe PH as a mPAP ≥35mmHg. Cardiac output (CO) was measured using the indirect Fick method with oxygen consumption estimated using the LaFarge equation. PVR was calculated as PVR=(mPAP–PCWP)/CO.

2.3.2 CT acquisition and ILD severity scoring

All patients were scanned from lung apices to bases, at full inspiration. Images of 1mm thickness were viewed at window settings optimized for the assessment of the lung parenchyma (width 1500 HU; level -500 HU). All images were reconstructed using a high spatial frequency, B70 kernel (Siemens, Munich, Germany). All CT scans were anonymized, and all reviewers were blinded to clinical data and outcome. The whole cohort's HRCT reconstructions were evaluated by two radiologists independently and patients were excluded from further study if there was either no ILD present or if the ILD severity affected less than 5% of the lung parenchyma. Severity of fibrosis was scored as: limited <20% or extensive >20%, and conflict of extent of fibrosis of more than one severity grade was resolved by consensus (Goh et al., 2008).

Additional scoring was also undertaken for a subset of the cohort (CTPA and prognostication studies) by one radiologist. A continuous scale was created which evaluated lobar fibrosis

extent (reticulation and honeycombing) to the nearest 5% for each lobe (figure 2.2). The individual lobar percentages were summed and divided by six (the lingula was considered a distinct lobe for ease of scoring) to create an average fibrosis score for each patient (Jacob et al., 2017b). The same technique was also employed to score the severity of emphysema, giving an overall score of emphysema.

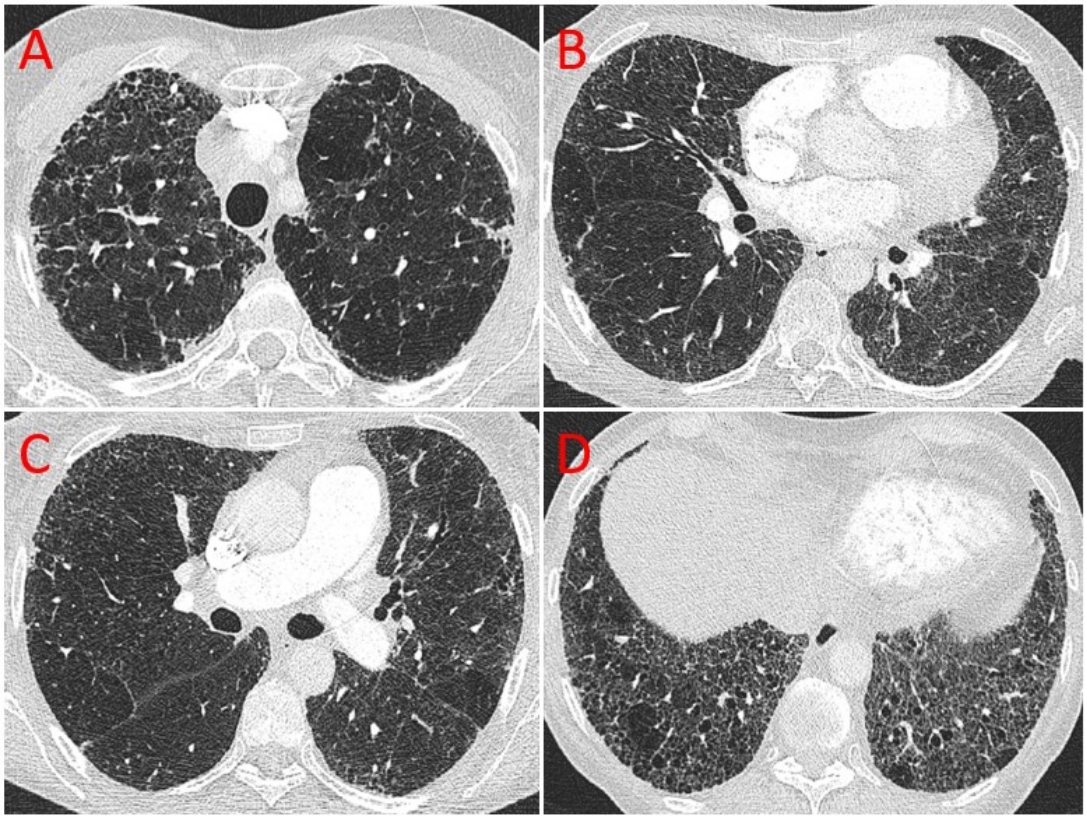


Figure 2.2. High resolution CT dicom's from a patient with an undiffertniated connective tissue disease associated ILD

A – The upper lobes, B – The middle lobe, C – The lingula, D – The lower lobes. ILD extent (reticulation and honeycombing) was scored at each lobe (lingula was treated as a distinct lobe for ease of scoring). The above patient ILD severity was scored as the sum of ILD extent in each of the six lobes which was summed and divided by 6 to give an overall ILD severity extent in percent. The workings for the above patient are included as an example below.

	Reticulation / Honeycombing	**Emphysema**
	(%)	**(%)**
Right upper lobe	35	15
Left Upper lobe	30	10
Middle lobe	40	20
Lingula	65	5
Right lower lobe	50	20
Left lower lobe	65	25
Sum of lobes	285	100
Overall extent	**48**	**17**

2.3.3 Main pulmonary artery and aorta measurements performed at CT

The MPAD and Ao was measured. Both contrast and non-contrast enhanced scans were used for measurement although where both had been performed during the same CT scan the MPAD was measured on the contrast CT. The axial section where the main pulmonary artery diameter bifurcated, was located using mediastinal windowing. Electronic callipers were used to measure the widest portion of the main pulmonary artery (Corson et al., 2014). The aorta was measured at the same level at its widest point. The MPAD:Ao ratio was then calculated (figure 2.3).

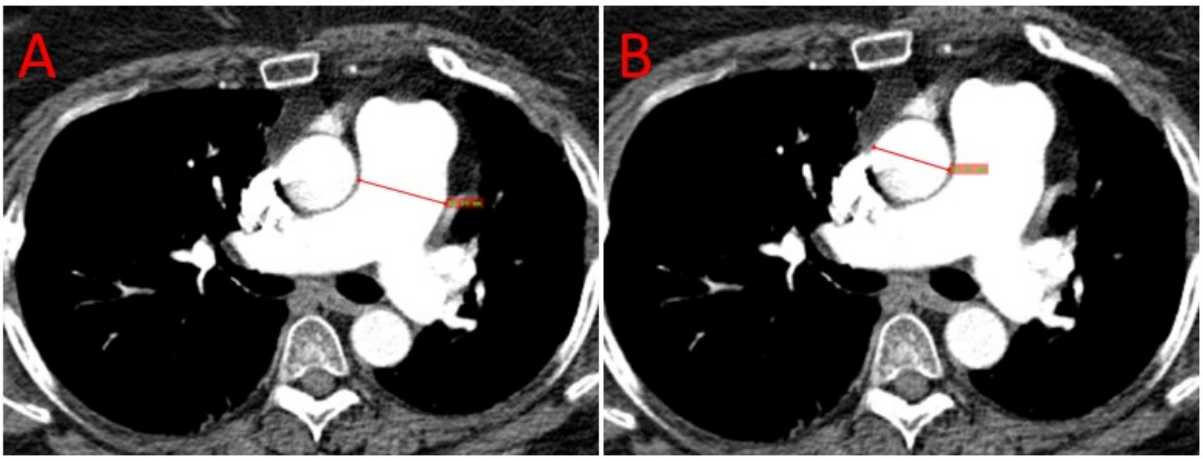


Figure 2.3. Measurement of the main pulmonary artery diameter and Aorta.

Panel A - Measurement of the main pulmonary artery diameter at its widest point at the bifurcation of the main pulmonary artery. Panel B - Measurement of the Aorta on the same axial level as the main pulmonary artery diameter. The above patient's main pulmonary artery measured 36.2mm and aorta measured 30.9mm. The main pulmonary artery diameter to aorta ratio was calculated thus: 36.2/30.9 = 1.17.

2.3.4 Measurements performed at CT pulmonary angiography

Where CT scans had been performed within six months of RHC detailed cardiac measurements were performed (figure 2.4). No image reconstruction was performed, and ECG gating was not used.

- The right ventricle (RV) was said to be "larger" or "smaller" than the LV using a subjective evaluation of cardiac chamber size where no measurements were performed, and the whole scan could be evaluated (Kumamaru et al., 2012).
- RV and LV diameter were measured at their widest point between the ventricular and interventricular endocardial wall (Contractor et al., 2002) at the mid-ventricular level, (Figure 2.4, panel 1), on the same CT level, which most closely resembled a four-chamber view and the RV:LV ratio calculated (RV:LV*axial*).
- The RV and LV diameters were also measured at their widest point (Reid and Murchison, 1998) at mid ventricular level (Figure 2.4, panel 2 and 3), and the RV:LV ratio calculated (RV:LV*largest*) (which could be measured on different axial CT levels).
- The right atrium (RA) was measured (Figure 2.4, panel 4) at the widest point between both the longitudinal (posterior border of the RA to level of the tricuspid annulus, RA*longitudinal*), and transverse plane (RA outer wall to the inter-atrial endocardial wall, RA*transverse*).
- Reflux of contrast media into the inferior vena cava (IVC) was scored as absent or present (Figure 2.4, panel 5).

- The left atrium (LA) was measured from the posterior endocardial border to the anterior endocardial border at its widest point (Figure 2.4, panel 6).
- Ventricular septal bowing was scored as present or absent based on whether the intraventricular septum was deviated into the LV (Figure 2.4, panel 7), or if it was deviated from its normal linear orientation (Figure 2.4, panel 8).

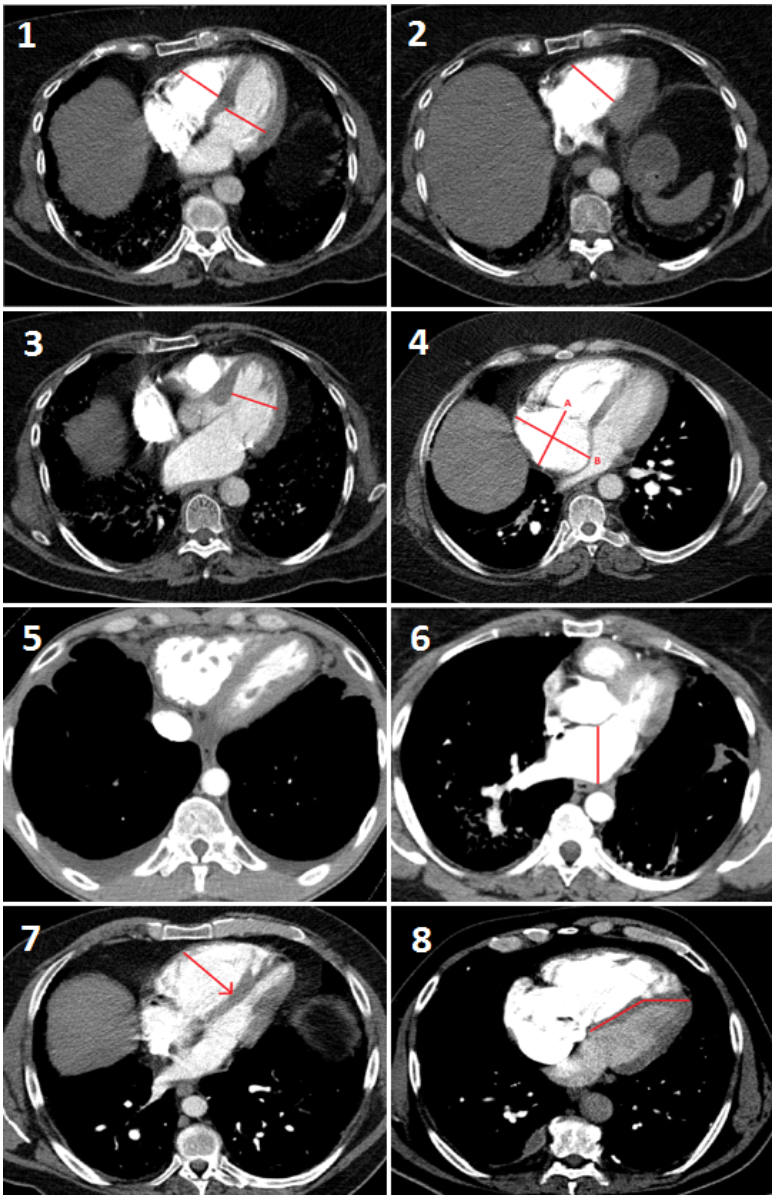


Figure 2.4. Measurements performed at CT pulmonary angiography

(1) The largest diameter of the right ventricle (RV) and left ventricle (LV) were measured at the mid-ventricular level at the level which most closely resembled a four-chamber view (and the RV:LV ratio calculated RV:LVaxial), the largest RV diameter (2) and LV diameter (3) were measured at the mid-ventricular level where it was largest (i.e. on different axial CT slices), and the RV:LV ratio calculated RV:LVlargest. The right atrium (RA) was measured (4) on both the longitudinal (A, delineated as the posterior border of the RA to the tricuspid annulus), and transverse planes (B, the widest point between RA walls). Reflux of contrast was graded as 0 where no reflux into the IVC was seen, or 1 where reflux into the IVC was present (5). The left atrium was measured (6) from its posterior to anterior border. The septum was said to be "bowed" if either it was deviated into the LV (7), or if the interventricular septum was deviated from its normal orientation (8).

2.3.5 Pulmonary function testing

Pulmonary function testing was performed with predicted values calculated using ATS/ERS criteria (1993). Measurements performed included spirometric (Miller et al., 2005) and single-breath diffusion capacity for the lung for carbon monoxide (TLco) and diffusion capacity adjusted for alveolar volume (Kco) (Macintyre et al., 2005). The composite physiological index (CPI) was created to reflect the morphological extent of pulmonary fibrosis at CT (Wells et al., 2003). The CPI was calculated for each patient [CPI = 91.0 - (0.65 x % predicted TLco) - (0.53 x % predicted FVC) + (0.34 x % predicted FEV1)] (Wells et al., 2003). Capillary bloods gas analysis was collected. The reference range for the partial pressure of oxygen (PaO_2) breathing room air is 10.6 – 13.3KPa, and partial pressure for carbon dioxide (pCO_2) is 4.7 – 6.0KPa. The inspired concentration was recorded, and the arterial alveolar gradient (AA gradient) calculated:

AA gradient = [Inspired O_2 (%) (atmospheric pressure – water vapour pressure) - $PaCO_2$ / 0.8] - PaO_2

2.3.6 Echocardiography

Images were acquired using a 3MHz frequency harmonic phased-array transducer. Doppler echocardiography was performed as per the American Society of Echocardiography recommendations (Rudski et al., 2010, Douglas et al., 2009). The 2D-echo datasets were interpreted by cardiologists with advanced echocardiography training (blind to clinical and haemodynamic data). The gradient between the RA and the RV was derived from the peak velocity of the tricuspid regurgitation (TRv). RA pressure was estimated based on IVC diameter and collapse. RVSP could be estimated by adding RA pressure to the pressure

differential between RA and RV in absence of pulmonary stenosis. The pulmonary flow acceleration time was obtained using pulsed Doppler in the right ventricular outflow tract close to the pulmonary valve in the parasternal short axis (PSAX) view and defined as the time from the onset of flow to peak velocity (Yared et al., 2011, Haddad et al., 2009). The mean pulmonary arterial pressure (PAP) and diastolic PAP were estimated using continuous wave Doppler of the pulmonary regurgitation (PR) jet in the PSAX view by measurement of the peak and minimal diastolic velocities. The tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode from the tricuspid lateral annulus (Matos et al., 2012). The myocardial systolic (TV s') velocity was obtained by placing a tissue Doppler sample volume at the lateral tricuspid annulus. We also calculated RV fractional area change (FAC) from the apical four chamber view using RV end-diastolic – RV end-systolic area / RV end-diastolic area. The eccentricity index was calculated as the ratio between the antero-posterior end the septo-lateral diameters of the left ventricle (LV) on a PSAX view (Ryan et al., 1985). The RV/LV ratio was obtained by using the antero-posterior diastolic diameters of the RV and the LV on a PSAX view. LA area and RA area were measured on apical four chamber view.

2.3.7 Brain natriuretic peptide

BNP was performed using a commercially available assay (normal value <20ng/L). BNP levels were collected where they had been performed within six months of RHC. Where BNP was a prognostic variable (Chapter 7 and 8 prognostication in ILD-PH) it was necessary to transform the data. As BNP levels were non-parametric the BNP was logged (natural logarithm). The data was analysed in its natural logarithm state and was transformed back

using the inverse of the natural logarithm, for further analysis (See specific chapter for further details).

2.4 Statistical Methods

All statistical analysis was performed using R version 3.3.1 (R Foundation for Statistical Computing). Data were summarised as number (percentage) for categorical variables and mean±SD or median [interquartile range, IQR] for continuous variables, as appropriate. Statistical tests used for each separate chapter are outlined as the results are presented in the following chapter. Table 2.1 shows the summary statistical tests used.

Distribution	Groups	Data type	Test
Parametric	2	Continuous	Student t-test
Non-parametric	2	Continuous	Wilcoxon Rank-Sum test
Non-parametric	2	Categorical	Chi-squared test (or where appropriate) Fisher's Exact test
Non-parametric	2	Categorical	Chi-squared test Post hoc testing (Chi-squared test with Bonferroni adjustment)
Parametric	>2	Continuous	Analysis of variance Post hoc testing Tukey honest significant difference (with adjusted p-values)
Parametric Non-parametric	>2	Continuous	Kruskal-Wallis test Post hoc testing (Wilcoxon Rank-Sum test with Bonferroni adjustment)

Table 2.1. Statistical tests used for summary statistics

Wilcoxon Rank-Sum test or Student's t-test was used for comparison of two groups, as appropriate. Continuous variables were compared between groups using Kruskal-Wallis test

(>2 groups) and post-hoc testing was performed with Wilcoxon Rank-Sum test with Bonferroni adjustment to p-values. For categorical variables, chi-squared or Fischer's exact test was used. Where there were >2 groups the Chi-squared test was used with post hoc Bonferroni adjustment to adjust for multiple testing of all pairs. A probability value (p) of <0.05 was considered as statistically significant. The whole cohort was used to assess the validity of the baseline data. The relationship of non-invasive variables and invasive haemodynamic data was assessed with Spearman rank correlation coefficients. Strength of correlation (r) was defined as follows: >0.5, large, 0.5 – 0.3, moderate 0.3 – 0.1 small and <0.1 trivial.

Validity in academic terms assesses the ability that conclusions drawn from a piece of work are valid. The validity of the data was assessed by comparing non-invasive variable values between PH severity (Chapter 3).

2.4.1 Comparison of continuous measurements and categorical measurements between 2 independent analysers

Continuous measurements were compared between two independent reviewers with Bland and Altman analysis. Bland-Altman analysis is widely performed to compare two clinical measurements to produce error measurements, or to compare a new method of measurement with the gold standard. The mean difference and range will be reported. Categorical measurements between analysers were compared by Cohen's Kappa which measures inter-rater agreement for categorical data. Kappa takes into the account the possibility that agreement could have occurred by chance. A Kappa value of 0.21-0.4 was considered fair, 0.41-0.6 was moderate, 0.61-0.80 was substantial and 0.81-1 as almost perfect agreement between reviewers.

2.4.2 Prediction of PH using non-invasive variables

Receiver operating curve (ROC) analysis was used to evaluate the ability of continuous variables to predict the presence of PH at RHC. The ability to predict both PH (mPAP at RHC ≥25mmHg, chapter 4), and severe PH (mPAP at RHC ≥35mmHg, chapter 5) was evaluated. Non-invasive variables were considered good predictors when their area under the curve (AUC) was >70. Non-inter-dependant variables were combined in a model to predict PH. A model consisting of echocardiographic variables to predict severe PH was derived and validated (further statistical details in specific chapters).

2.4.3 Survival analysis and prognostication in ILD-PH

Survival analysis was performed using Cox proportional hazards regression. Kaplan-Meier survival analysis was used to estimate and plot survival. Follow up time for mortality analysis was from the date of the RHC (Unless otherwise specified in each chapter), until either the primary outcome (death or lung transplant) occurred or the patients were censored at last contact. Mortality was screened for using the NHS Spine portal (date of last screen 12/10/2018).

2.5.1 Patient demographics

Over the study period, 303 patients formed the ILD-PH cohort (Table 2.2). ILD diagnoses included IPF (n=75), CTD-ILD (n=107), sarcoidosis (n=54), CHP (n=26), NSIP (n=20) and "Other" ILDs (n=21). The diagnostic groups which make up the CTD-ILD and other ILD groups are shown in (Table 2.3). Mean age at RHC was 61±11 years of age. Patients with IPF were older than patients with a CTD-ILD ($p<0.001$), and patients with sarcoidosis ($p<0.001$). 49% of the whole cohort was male although, there were significantly more men in the IPF patient

group (79%), and less men in the CTD-ILD cohort (35%), ($p<0.001$). Body mass index (BMI) was not significantly different between the different ILD groups ($p=0.9$). There was a trend toward the "other" ILD group being more likely to be current smokers, and patients with CHP having the lowest number of pack years, although on inter-group analysis a significant difference could not be found. Patients with CTD-ILD were less likely to be prescribed long term oxygen therapy (LTOT) ($p<0.001$). There was no difference in FC between the ILD groups. The indication for patients to be referred to the PH team was known in 258 (85%) of the 303 patients and was due to: clinical signs of PH at echocardiography in 227 (88%), pulmonary function test abnormalities in 18 (7%), and elevated BNP in 13 (5%).

	Whole Cohort	IPF	CTD-ILD	Sarcoid	CHP	NSIP	Other ILD	p-value
Number	303	72	107	54	26	20	24	-
Age	61±11	66±11	59±11	59±10	59±13	62±11	60±13	<0.001
Gender (%, men)	49	79	35	50	38	45	50	<0.001
BMI (kg/m²)	26±6	27±6	26±6	27±6	29±6	29±6	25±6	0.9
Current smoker (%)≠	23	34	14	25	9	20	36	0.02
Ex-smoker (%)≠	36	36	36	40	22	53	36	0.5
Pack-years ≠	11±14	15±15	9±12	7±13	4±7	14±16	17±16	0.002
LTOT prescription (%) ‡	68	79	54	60	73	95	87	<0.001
Functional class † (% in FC: II / III/IV)	4/84/12	0/78/22	6/84/10	2/93/5	8/76/16	5/90/5	4/83/13	0.5

Table 2.2. Demographic information for the whole cohort and individual ILD diagnostic groups.

Abbreviations: IPF - Idiopathic pulmonary fibrosis, CTD-ILD - connective tissue disease associated interstitial lung disease, CHP - chronic hypersensitivity pneumonitis, NSIP - non-specific pneumonitis, RHC - right heart catheter, BMI - body mass index, LTOT - long term oxygen therapy. Continuous data was analysed with Kruskal-Wallis test and post-hoc testing was performed with Wilcoxon Rank-Sum test with Bonferroni adjustment to p-values. For categorical variables, chi-squared with post hoc Bonferroni adjustment to adjust for multiple testing of all pairs. ≠ Smoking status was known in n=246 (81%) of the cohort. ‡ LTOT prescription was known in n=299 (99%) of the cohort. Functional class was known in n=293 (97%) of the cohort.

Specific CTD-ILD diagnoses	Number	Other ILD diagnoses	Number
Scleroderma	47	Smoking related ILD	5
Antisynthetase / PM / DM	15	Unclassifiable ILD	7
UCTD	14	Lymphangioleiomyomatosis	2
Rheumatoid arthritis	13	Pleuro-parenchymal fibro-elastosis	2
Mixed connective tissue disease	12	Fibrotic organising pneumonia	1
Sjogren's syndrome	4	Langerhans cell histiocytosis	3
Systemic lupus erythematous	2	Pulmonary alveolar proteinosis	1
Total	107	Total	21

Table 2.3. CTD-ILD and Other ILD diagnoses

Abbreviations: PM - Polymyositis, DM - Dermatomyositis, UCTD - Undifferentiated connective tissue disease.

2.5.2 Pulmonary function tests at RHC

286 (94.3%) patients had baseline pulmonary function tests (PFT's) performed (table 2.4). Median interval between RHC and PFT was -0.6[-2.2 – 0.0] months. Mean FEV_1 was 1.6±0.6L, 58±18% predicted. FEV_1 (% predicted) was significantly lower in patients with sarcoid 51±14% predicted versus IPF patients 61±16% predicted, (p=0.02), and CTD-ILD 62±18% predicted, (p=0.006). Mean FVC was 2.0±0.8L, 60±20%. FVC was not significantly different between the groups, however there was a trend towards patients with CHP having reduced FVC although this was not significant when evaluating between diagnostic groups. Mean TLco was 26±10% predicted. Patients with IPF had lower TLco 22±7% predicted than patients with CTD-ILD 27±10% predicted, (p=0.03), and sarcoid 30±13% predicted, (p=0.02). Patients with "other" ILDs TLco 21±19% predicted was also lower than patients with CTD-ILD 27±10% predicted, (p=0.03), and sarcoid 30±13% predicted, (p=0.03). Mean Kco was 53±17% predicted, and patients with "other" ILDs 41±19% predicted had lower Kco levels than patients with CTD-ILD 54±15% predicted, (p=0.03), and sarcoid 56±16% predicted, (p=0.03). The mean CPI was 62±11, and patients with IPF had significantly higher CPI 66±7 versus patients with sarcoid 55±14 (p<0.001). Capillary blood gas analysis was performed in 238 (76.2%). Mean PaO_2 was 8.0±2.0kPa, patients with IPF 7.2±1.5 kPa were more hypoxaemic than patients with CTD-ILD 8.9±2.0 kPa (p<0.001) and patients with sarcoid 8.3±1.8 kPa (p=0.04). The mean $PaCO_2$ was 5.1±0.8 kPa. Patients with CHP had higher $PaCO_2$ 5.6±1.1 kPa than patients with CTD-ILD 4.8±0.7 kPa (p=0.02). The mean Aa gradient was 5.9±2.9kPa. Patients with IPF had higher Aa gradient 6.4±1.8 kPa than patients with CTD-ILD 5.3±3.0 kPa (p=0.02).

	Whole Cohort	IPF	CTD-ILD	Sarcoid	CHP	NSIP	Other ILD	p-value
Number	289	75	99	50	26	18	21	-
FEV_1 (Litres)	1.6±0.6	1.7±0.6	1.6±0.5	1.4±0.5	1.5±0.9	1.5±0.7	1.5±0.6	0.02
FEV_1 (% predicted)	58±18	61±16	62±18	51±14	52±21	57±20	56±21	0.001
FVC (Litres)	2.0±0.8	2.0±0.7	2.0±0.8	2.2±0.9	1.6±0.7	1.9±1.0	2.1±0.8	0.06
FVC (% predicted)	60±20	58±17	63±20	63±20	52±21	59±20	63±22	0.05
TLco (% predicted)	26±10	22±7	27±10	30±13	24±10	25±9	21±9	<0.001
Kco (% predicted)	53±17	51±15	54±15	56±16	55±20	51±13	41±19	0.02
CPI	62±11	66±7	61±10	55±14	65±10	61±10	63±11	<0.001
Capillary blood gas analysis								
Number	232	60	82	38	21	15	16	-
PaO_2 (kPa)	8.0±2.0	7.2±1.5	8.9±2.0	8.3±1.8	7.6±2.3	7.3±1.7	7.5±2.2	<0.001
$PaCO_2$ (kPa)	5.1±0.8	5.1±0.7	4.8±0.7	5.1±0.8	5.6±1.1	5.1±1.1	5.1±0.8	0.03
Arterial alveolar gradient (kPa)	5.9±2.9	6.4±1.8	5.3±3.0	5.3±1.8	5.4±2.2	7.9±5.5	7.0±4.0	0.003

Table 2.4. Pulmonary function tests in the whole cohort and in individual ILD diagnostic groups

Abbreviations: FEV_1 - forced expiratory volume, FVC - forced vital capacity, TLco - gas transfer, Kco - gas transfer adjusted for alveolar volume, CPI - composite physiological index, PaO_2 - partial pressure of oxygen, $PaCO_2$ - partial pressure of carbon dioxide. Statistical tests used as per table 2.2.

2.5.3 Brain natriuretic peptide at RHC

278 (91.7%) patients had a brain natriuretic peptide performed at RHC, median interval from RHC 0[-0.8 - 0] months (table 2.5). Median BNP in the whole cohort was 102 [42 - 265] ng/L. There was no significant difference between the ILD groups in terms of BNP levels performed at the time of the RHC (p=0.4)

	Whole Cohort	IPF	CTD-ILD	Sarcoid	CHP	NSIP	Other ILD	p-value
Number	278	72	89	51	25	20	21	-
BNP (ng/L)	102 [42 – 265]	82 [45 – 234]	133 [42 – 266]	126 [49 – 365]	48 [35 – 128]	73 [47 – 218]	96 [45 – 271]	0.4

Table 2.5. Brain natriuretic peptide levels in the whole cohort and in individual ILD diagnostic groups

Abbreviations as per table 2.2. Statistical tests used as per table 2.2.

2.5.4 Echocardiography at RHC

285 (94%) patients had an echocardiogram at RHC, median interval -0.8[-1.9 – 0] months (table 2.6). Mean TRv was 3.7±0.7m/s and was available in 92% of studies performed. Mean RVSP was 65±21mmHg (normal = 15 – 25mmHg), and mean RA area was 19cm² (normal < 18cm²). The mean RV:LV ratio (diastolic short axis view) was 0.8±0.4 (normal = 0.5 – 0.7). Mean pulmonary acceleration time was 77±19ms (normal >130m/s). Mean FAC of the right ventricle was 37±8 (normal = 32 – 60%). There was no statistical difference in echocardiographic variables between the ILD groups.

	Whole Cohort	IPF	CTD-ILD	Sarcoid	CHP	NSIP	Other ILD	p-value
Number	285	72	95	53	25	20	21	-
TRv maximum (m/s)	3.7±0.7	3.7±0.5	3.7±0.7	3.8±0.8	3.7±0.6	3.7±0.5	4.0±0.7	0.5
RVSP (mmHg)	65±21	64±17	63±22	70±24	64±20	64±12	74±23	0.2
RA area (cm^2)	19±8	20±8	19±8	18±7	19±6	19±6	20±9	0.9
RV:LV ratio (diastolic)	0.84±0.4	0.81±0.4	0.85±0.4	0.89±0.6	0.83±0.4	0.85±0.3	0.80±0.3	0.9
Pulmonary acceleration time (ms)	77±19	80±16	79±22	77±19	74±16	70±15	73±20	0.2
FAC (%)	37±8	37±9	37±8	36±8	38±7	37±8	34±7	0.5
TAPSE (mm)	18±5	19±5	17±5	18±4	18±5	18±5	17±4	0.3

Table 2.6. Echocardiography in the whole cohort and in individual ILD diagnostic groups

Abbreviations: TRv - maximum tricuspid regurgitation maximum, RA - right atrial, RVSP - right ventricular systolic pressure, FAC - fractional area change, TAPSE - trans annular systolic planar excursion. Statistical tests used as per table 2.2.

2.6 Haemodynamics at RHC

Mean pulmonary arterial pressure was 33±11mmHg (Table 2.7). Sarcoid patients had higher mPAP 38±12mmHg compared to patients with IPF 31±10mmHg (p=0.005), CTD-ILD 32±11mmHg (p=0.03). Patients in the "other" ILD group also had higher mPAP than patients with IPF 31±10mmHg (p=0.05). PH was present in 238 (78.5%) of the cohort and was mild-moderate PH (mPAP ≥25mmHg and <35mmHg) in 109 patients (35.9%), and severe (mPAP ≥35mmHg) in 129 patients (42.5%). Mean cardiac output (CO) was 4.2±1.3L/m with no significant differences seen between the subgroups. Mean PVR was 6.2±4.1 Wood units, sarcoid patients PVR was 8.1±5.1 higher than patients with IPF 5.4±3.8 Wood units (p=0.01) and CTD-ILD patients 5.8±3.9 Wood units (p=0.05).

	Whole Cohort	IPF	CTD-ILD	Sarcoid	CHP	NSIP	Other ILD	p-value
Number	303	72	107	54	26	20	24	-
mPAP (mmHg)	33±11	31±10	32±11	38±12	30±12	34±7	37±11	<0.001
PH (%) (≥25mmHg)	78.5	74	73	91	62	95	96	0.001
Severe PH (%) (≥35mmHg)	42.5	31	38	59	42	45	54	0.04
CO (L/m)	4.2±1.3	4.4±1.4	4.3±1.3	3.9±1.1	4.4±1.4	3.7±1.2	4.4±1.6	0.2
PCWP (mmHg)	9±5	10±5	10±4	10±6	8±5	12±8	9±4	0.2
PVR (Wood units)	6.2±4.1	5.4±3.8	5.8±3.9	8.1±5.1	6.2±4.6	6.7±3.8	6.3±2.4	0.01

Table 2.7. Right heart catheter haemodynamics in the whole cohort and in individual ILD diagnostic groups

Abbreviations: mPAP - mean pulmonary arterial pressure, PH - pulmonary hypertension, CO - cardiac output, PCWP - pulmonary capillary wedge pressure, PVR - pulmonary vascular resistance. Statistical tests used as per table 2.2.

2.7 Survival in the cohort

Median follow up time in the cohort was 2.50[1.0–4.6] years. Over follow-up 239 (78.8%) died or underwent lung transplant; 223 (73.5%) patients died and 16 patients (5%) underwent lung transplant (Figure 2.5, panel A). The underlying ILD sub-type heavily influenced prognosis (Figure 2.5, panel B), with patients with IPF having the worst prognosis. A diagnosis of PH was a negative prognostic factor (Figure 2.5, panel C), although when patients were stratified into mild-moderate PH and severe PH, patients with severe and mild-moderate had similar prognoses (Figure 2.5, panel D).

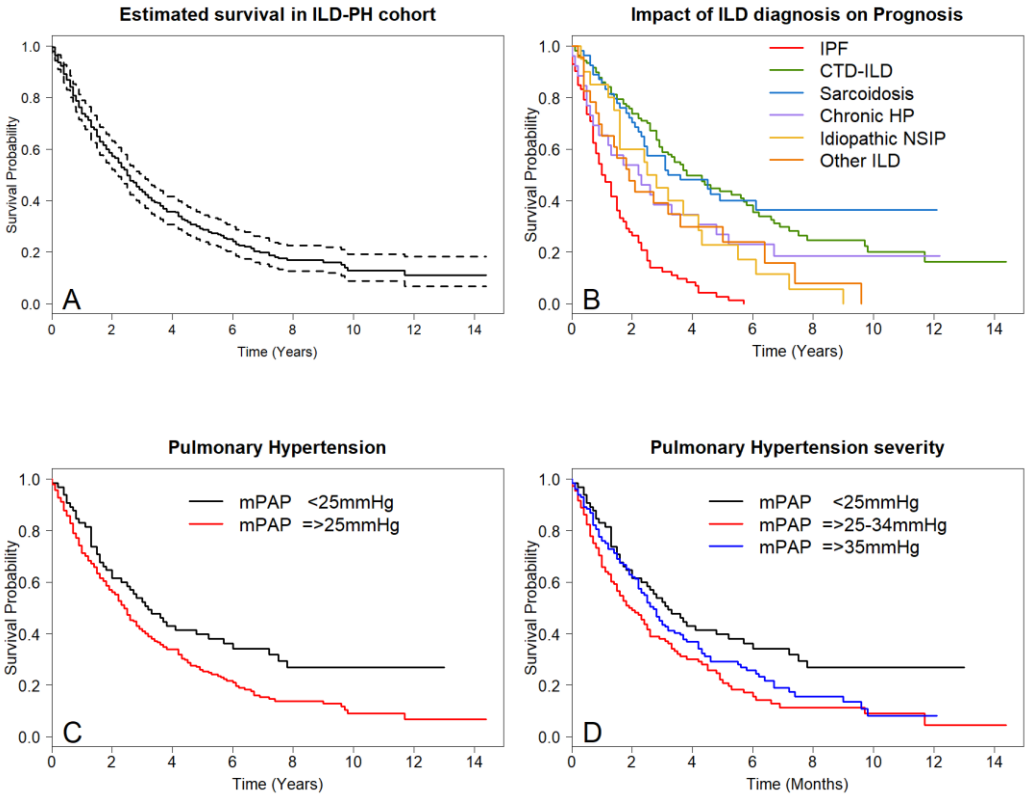


Figure 2.5. Kaplan-Meier survival estimates.

Panel A - Survival estimates for the whole ILD-PH cohort, Panel B - Survival in the ILD-PH cohort stratified by ILD diagnosis, Panel C - Survival in the ILD-PH cohort stratified by PH status, Panel D - Survival in the ILD-PH cohort stratified PH severity. Abbreviations as per table 8.2.

2.8 Treatment with vasodilators

167 patients were treated with vasodilator therapy, this constituted treatment of 70% of patients with PH at RHC. There were several therapeutic drug trials throughout this trial period. RBH was a major centre for the multi-centre bosentan in pulmonary hypertension associated with fibrotic interstitial pneumonia (BPHIT) trial. In total there was 31 patients on the BPHIT trial and 2 patients on the Efficacy and safety in patients with symptomatic PH associated with IIP (RISE). These trials are responsible for a high number of the IIP patients being treated. The large number of patients with CTD-ILD and sarcoid (where use of vasodilators is accepted within the National PH Commissioned Service) also contributes to the large number of patients on treatment. Figure 2.6, panel A shows that the prescription of vasodilators increases as mPAP at RHC increases. Of 129 patients with severe PH 108 (84%) were treated with vasodilators, whereas in 109 patients with mild-moderate PH 55 (50%) were treated ($p<0.001$). Even despite the clinical trials IPF patients were less likely to receive vasodilators if diagnosed with PH at RHC ($p<0.001$). Figure 2.6, panel B demonstrates the influence of ILD diagnosis on receiving vasodilators. Mortality (and most likely advanced disease status and frailty) also impacted on the ability of patients to receive treatment, with patients who died less than a year after RHC being much less likely to receive treatment ($p<0.001$) despite having PH at RHC (Figure 2.6, panel C). The Kaplan-Meier plot in Figure 2.6, panel D, suggests that treatment with vasodilators in patients with PH is associated with an improved short-term outcome. Although the decision to treat was so strongly linked to ILD sub-type, PH severity and short-term mortality that no inference of benefit with the use of vasodilators can be confirmed in this cohort.

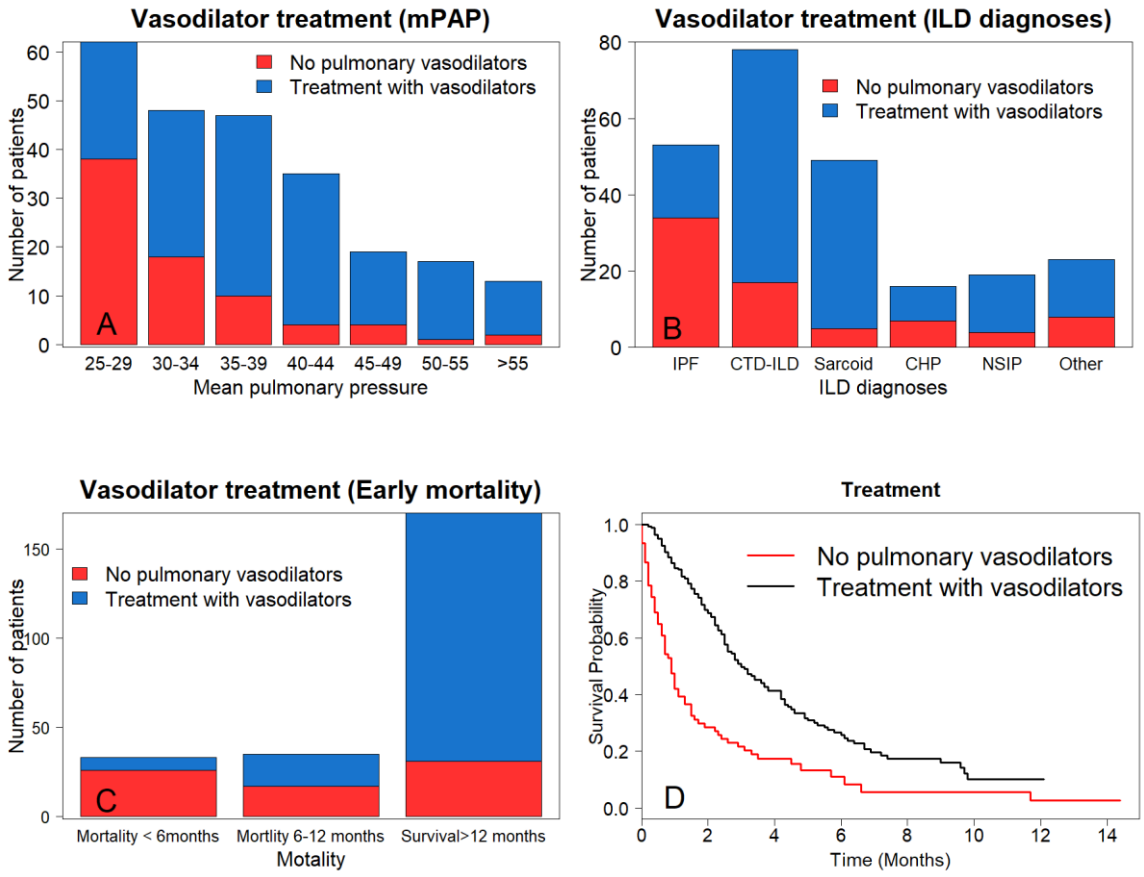


Figure 2.6. Bar-plots demonstrating the influence of ILD subtype and PH severity on treatment with vasodilators.

Panel A - Bar-plot showing the influence of PH severity on decision to use vasodilators, Panel B - Bar-plot showing the influence of ILD subtype on decision to use vasodilators, Panel C - Bar-plot showing that patients who experienced early mortality were less likely to be treated with vasodilators. Panel D - Kaplan-Meier plot showing higher risk of mortality in patients who did not receive treatment with vasodilators. Abbreviations as per figure 2.5.

2.9 Discussion

The full cohort of 303 patients is to my knowledge the largest collective cohort of ILD patient who have undergone RHC studies. All CT scans were reviewed by 2 radiologists to ensure that patients had ILD. This is important particularly in patients with CTD-ILD and sarcoid as they can develop a PAH primarily affecting the pulmonary arteries. Severity of

fibrosis and emphysema was also scored in a more detailed continuous fashion in studies of prognostication. This was both to evaluate the effect of fibrotic burden of disease and to try and prevent confounding of reliance upon pulmonary function tests to adjust for ILD severity (which would be affected by both fibrotic burden and PH). All patients underwent RHC evaluation whereas other cohorts have relied upon RVSP estimated at echocardiogram which has been shown to both over and underestimate pulmonary arterial pressure (Arcasoy et al., 2003), and a reliable threshold to reliably predict PH could not be found (Nathan et al., 2008b).

Lung function was similar between all the groups with sarcoid having lower FEV_1 than patients with CTD-ILD and IPF, which is probably explained by a higher prevalence of small-airway involvement in sarcoid particularly in advanced disease. Overall FVC looked to be reduced in patients with CHP although no significant difference could be demonstrated on testing between the groups. TLco was lower in patients with IPF and the "other" ILD group compared to CTD-ILD group and sarcoid group. This is likely to be explained by worse ILD severity and co-existence of emphysema in the "other" ILD group and will be explored further in the next chapter.

All patients who underwent RHC had a strong clinical suspicion of PH which in 85% of the patients was due to signs of PH at echocardiography. PH was very prevalent in the cohort (78.5%) due to extremely high pre-test probability of PH, in this cohort. Sarcoid had higher mPAP and PVR compared to patients with IPF and CTD-ILD, and the "other" ILD group also had higher mPAP than patients with IPF. The high prevalence of PH in sarcoidosis may be explained by the fact that sarcoidosis has multiple methods of causing PH both through

direct vascular involvement, extrinsic compression by lymph nodes, cardiac involvement as well as parenchymal fibrosis. Higher mPAP in the "other" ILD group may be explained by a higher burden of emphysema as unclassifiable, smoking related ILD and Langerhans predominate in this group.

The largest patient groups in the cohort are IPF, CTD-ILD and sarcoidosis which between them make up n=235 (78%) of the cohort. This initial analysis of baseline demographics, echocardiography and haemodynamics demonstrates that the similarities between the groups are much greater than the differences which support the methodology of combining the patients within a larger cohort for further evaluation.

Follow up to lung transplant or death was complete in nearly three quarters of the entire cohort (73.8%). Baseline ILD diagnosis strongly influences prognosis, with IPF patients experiencing the worst prognosis. Sarcoid and CTD-ILD patients had very similar prognoses, and NSIP and "other" ILDs were again similar in their longitudinal trends in mortality. PH was a negative prognostic factor despite its extremely high prevalence, and relative lack of patients without PH for adequate comparison.

Treatment appears to improve the outcome of patients with ILD-PH, although treatment decisions in our cohort were strongly liked to baseline disease severity and ILD subtype which has biased toward treatment having a beneficial effect. Treatment with vasodilators was much more likely when pressures were severe with 84% treated with severe PH treated versus 49% treated in the non-severe PH group ($p<0.001$). Patients with IPF were also significantly less likely to be prescribed vasodilator treatment. Finally, patients with PH often

unfortunately died shortly after RHC preventing them from having time to receive vasodilator therapy, and again leads to a bias toward vasodilator therapy being effective.

Chapter 3 Exploration of the cohort – correlation of non-invasive investigations with haemodynamics

3.1 Rationale

It is highly desirable to identify the non-invasive markers which best correlate with PH so that we can infer the contributing factors to ILD-associated PH and to develop a non-invasive screening tool to identify individual patients to undergo further evaluation for ILD-associated PH. Also, by understanding the correlation and inter-dependence of variables we may be able to infer the cause of PH occurring in ILD.

3.2 Methods

The cohort previously described was used in analysis to assess correlation of non-invasive markers with invasive haemodynamics. Spearman's correlation co-efficient was used to assess correlation of non-invasive markers with mPAP and PVR. Strength of correlation was assessed by <0.1 – minimal to no effect, ≥0.1-0.29 – weak correlation, ≥0.3-0.49 moderate correlation and ≥0.5 a strong correlation. Patients were tested as a whole cohort and separated into two groups (Group 1 – IPF + CHP + "Other" ILD), and (Group 2 – CTD-ILD + Sarcoid + NSIP).

The cohort was compared based upon PH severity, with patients with mPAP >25mmHg compared to patients with no PH. Non-invasive variables were compared between groups with student t-test or Wilcoxon Rank-sum test as appropriate. Patients were also compared between PH severity groups with patients without PH being compared with patient with

mild-moderate PH (mPAP ≥25-34), and severe PH (mPAP ≥35). Patients were compared with analysis of variance analysis (ANOVA), with post hoc testing by tukey honest significant difference, and Kruskal-Wallis, and post hoc testing was with the Wilcoxon Rank-sum test with Bonferroni adjustment due to multiple testing.

3.3 Correlation of non-invasive variables with mean pulmonary arterial pressure and pulmonary vascular resistance measured at right heart catheter

3.3.1 Correlation of pulmonary function tests with invasive haemodynamics

Spirometric measures (FEV_1 and FVC), showed no correlation with invasive haemodynamics (Table 3.1). TLco showed a weak correlation with mPAP (r= -0.26, p<0.001), and a moderate correlation with PVR (r= -0.34, p<0.001). Kco showed a moderate correlation with mPAP (r=-0.32, p<0.001), and PVR (r= -0.40, p<0.001). The CPI showed no correlation with either mPAP or PVR. A ratio comprised of the FVC/TLco showed a weak correlation with mPAP (r= 0.25, p<0.001), and moderate correlation with PVR (r= 0.35, p<0.001). PaO_2 showed moderate correlation with mPAP (r= -0.44, p<0.001), and PVR (r= -0.39, p<0.001). Patients with CTD-ILD / sarcoid showed a stronger correlation with mPAP (r= -0.58, p<0.001) and with PVR (r= -0.53, p<0.001), compared to patients with IIP / CHP which correlated less strongly with mPAP (r= -0.41, p<0.001), and PVR (r= -0.35, p<0.001). The same trend was noted with the Aa gradient although the difference between IIP/CHP patients and patients with CTD-ILD was smaller.

	PFT variable	Whole cohort		IIP / CHP		CTD-ILD / sarcoid	
		r	p value	r	p value	r	p value
mPAP	FEV_1 % pred	-0.117	0.06	-0.132	N/S	-0.114	N/S
	FVC % pred	0.004	N/S	0.03	N/S	-0.02	N/S
	TLco % pred	-0.264	<0.001	-0.277	0.002	-0.284	<0.001
	Kco % pred	-0.32	<0.001	-0.35	<0.001	-0.31	<0.001
	CPI	0.07	N/S	0.02	N/S	0.13	N/S
	FVC/TLco ratio	0.25	<0.001	0.29	<0.001	0.24	0.004
	PaO2	-0.44	<0.001	-0.41	<0.001	-0.58	<0.001
	Aa gradient	0.49	<0.001	0.50	<0.001	0.56	<0.001
PVR	FEV_1 % pred	-0.05	N/S	-0.02	N/S	-0.08	N/S
	FVC % pred	0.04	N/S	0.08	N/S	-0.01	N/S
	TLco % pred	-0.34	<0.001	-0.32	<0.001	-0.38	<0.001
	Kco % pred	-0.40	<0.001	-0.42	<0.001	-0.41	<0.001
	CPI	0.11	N/S	0.06	N/S	0.21	0.02
	FVC/TLco ratio	0.35	<0.001	0.37	<0.001	0.38	<0.001
	PaO2	-0.39	<0.001	-0.35	<0.001	-0.53	<0.001
	Aa gradient	0.45	<0.001	0.42	<0.001	0.55	<0.001

r = Spearman correlation coefficient

<0.1 no effect	≥0.1 weak	≥0.3 moderate	≥0.5 strong	Positive
<0.1 no effect	≥0.1 weak	≥0.3 moderate	≥0.5 strong	Negative

Table 3.1. Spearman's correlation co-efficient for pulmonary function tests and invasive haemodynamics. In the whole cohort and stratified by ILD subtype.

Abbreviations: PFT - Pulmonary function test, r - Spearman's correlation co-efficient, IIP - Idiopathic interstitial pneumonia, CHP - chronic hypersensitivity pneumonitis, CTD - connective tissue disease, mPAP - mean pulmonary artery pressure, PVR - Pulmonary vascular resistance, FEV_1 - Forced expiratory volume in one second, pred - Predicted, FVC - Forced vital capacity, TLco - Gas transfer, Kco - gas transfer co-efficient, CPI - Composite physiological index, PaO2 - partial pressure of oxygen, Aa - gradient Alveolar arterial gradient, N/S - non-significant.

3.3.2 Correlation of CT measured variables with invasive haemodynamics

MPAD showed moderate correlation with mPAP (r= 0.41, p<0.001), and weak correlation with PVR (r= 0.28, p<0.001), CTD-ILD / Sarcoid correlated more strongly than patients with IIP / CHP (Table 3.2). In the whole cohort MPAD:Ao correlated moderately with mPAP (r= 0.31, p<0.001), although this was primarily driven by moderate correlation in the CTD-ILD/sarcoid group which showed moderate correlation (r= 0.48, p<0.001), whereas no correlation was seen in the IIP/CHP group. This trend was the same for MPAD:Ao ratio and PVR, with CTD-ILD/sarcoid showing modest correlation (r= 0.41, p<0.001), and no correlation was shown in the IIP/CHP group. Neither CT lobar severity of fibrosis nor extent of emphysema correlated. CT lobar severity of fibrosis was summed with emphysema extent and again no correlation with invasive haemodynamics was demonstrated.

	CT variable	Whole cohort		IIP / CHP		CTD-ILD / sarcoid	
		r	p value	r	p value	r	p value
mPAP	MPAD	0.41	<0.001	0.34	<0.001	0.48	<0.01
	MPAD:Ao	0.31	<0.001	0.12	N/S	0.48	<0.001
	ILD extent	-0.04	N/S	-0.12	N/S	0.06	N/S
	Emph extent	0.10	N/S	0.12	N/S	0.13	N/S
	ILD + Emph	0.01	N/S	0.03	N/S	0.07	N/S
PVR	MPAD	0.28	<0.001	0.14	0.1	0.42	<0.001
	MPAD:Ao	0.20	0.002	-0.05	0.05	0.41	<0.001
	ILD severity	0.02	N/S	-0.07	N/S	0.14	N/S
	Emph severity	0.04	N/S	0.04	N/S	0.06	N/S
	ILD + Emph	-0.01	N/S	-0.06	N/S	0.10	N/S
r = Spearman correlation coefficient							
<0.1 no effect	≥0.1 weak	≥0.3 moderate		≥0.5 strong		Positive	
<0.1 no effect	≥0.1 weak	≥0.3 moderate		≥0.5 strong		Negative	

Table 3.2. Spearman's correlation co-efficient for CT variables in the whole cohort and separated by ILD subtype.

Abbreviations MPAD - Main pulmonary artery diameter, MPAD:Ao - Main pulmonary artery to aorta ratio, ILD interstitial lung disease, Emph - Emphysema otherwise as per table 3.1.

3.3.3 Correlation of Brain natriuretic peptide with invasive haemodynamics

BNP levels demonstrated a strong correlation with both mPAP (r=0.58, p<0.001) and PVR (r=0.57, p<0.001). There was no difference between patient groups (Table 3.3).

		Whole cohort		IIP / CHP		CTD-ILD / sarcoid	
		r	p value	r	p value	r	p value
mPAP	BNP	0.58	<0.001	0.54	<0.001	0.59	<0.001
PVR	BNP	0.57	<0.001	0.56	<0.001	0.57	<0.001

r = Spearman correlation coefficient				
<0.1 no effect	≥0.1 weak	≥0.3 moderate	≥0.5 strong	Positive
<0.1 no effect	≥0.1 weak	≥0.3 moderate	≥0.5 large	Negative

Table 3.3. Spearman's correlation co-efficient for BNP levels in the whole cohort and separated by ILD subtype.

Abbreviations: BNP - Brain natriuretic peptide, otherwise as per table 3.1.

3.3.4 Correlation of Echocardiographic measurements with invasive haemodynamics

Measures of right ventricular systolic pressure, TRv (r=0.53, p<0.001) and RVSP (r= 0.54, p<0.001) showed strong to moderate correlation with mPAP (r= 0.47, p<0.001), and PVR (r=0.48, p<0.001) (table 3.4). Eccentricity index showed strong correlation with mPAP (r= 0.0.55, p<0.001), and PVR (r= 0.56, p<0.001). RA area also showed moderate correlation with mPAP (r= 0.49, p<0.001), and PVR (r= 0.44, p<0.001). FAC showed a moderate negative correlation with mPAP (r= -0.47, p<0.001), and with PVR (r= -0.40, p<0.001). The RV:LV ratio showed strong correlation, with mPAP (r=0.53, p<0.001), and with PVR (r=0.54, p<0.001).

	Echo variable	Whole cohort		IIP / CHP		CTD-ILD / sarcoid	
		r	p value	r	p value	r	p value
mPAP	TRv	0.53	<0.001	0.48	<0.001	0.57	<0.001
	RVSP	0.54	<0.001	0.50	<0.001	0.58	<0.001
	Eccentricity index	0.55	<0.001	0.52	<0.001	0.58	<0.001
	Right Atrial Area	0.49	<0.001	0.55	<0.001	0.45	<0.001
	FAC	-0.47	<0.001	-0.42	<0.001	-0.52	<0.001
	Pull acc time	-0.35	<0.001	-0.28	<0.001	-0.40	<0.001
	RV:LV ratio	0.53	<0.001	0.51	<0.001	0.55	<0.001
PVR	TRv	0.47	<0.001	0.49	<0.001	0.47	<0.001
	RVSP	0.48	<0.001	0.49	<0.001	0.49	<0.001
	Eccentricity index	0.56	<0.001	0.50	<0.001	0.62	<0.001
	Right Atrial Area	0.42	<0.001	0.47	<0.001	0.39	<0.001
	FAC	-0.40	<0.001	-0.34	<0.001	-0.44	<0.001
	Pull acc time	-0.34	<0.001	-0.31	0.001	-0.36	<0.001
	RV:LV ratio	0.54	<0.001	0.45	<0.001	0.61	<0.001
r = Spearman correlation coefficient							
<0.1 no effect	≥0.1 small effect	≥0.3 moderate effect		≥0.5 large effect		Positive	
<0.1 no effect	≥0.1 small effect	≥0.3 moderate effect		≥0.5 large effect		Negative	

Table 3.4. Spearman's correlation co-efficient for Echocardiographic measurements in the whole cohort and separated by ILD subtype.

Abbreviations: Echo - Echocardiography, TRv - Tricuspid regurgitation velocity, RVSP - Right ventricular systolic pressure, FAC - Fractional area change, Pull acc time - Pulmonary acceleration time, RV:LV - Right ventricle to Left ventricle ratio, otherwise as per table 3.1.

3.4 PH versus No-PH

3.4.1 Demographic, haemodynamics and CT metrics

Patients have been stratified by PH status in table 3.5. There was no difference in age at RHC (p=0.6), or gender (p=0.9) between patients with and without PH. The prescription of LTOT was more common in patients with PH (76% versus 39%, p<0.001). MPAD was larger in patients with PH 34.4±4mm versus 30.1±5mm (p<0.001), and MPAD:AA ratio was significantly larger in patients with PH (p<0.001). There was no difference in the number of patients who had an extent of fibrosis of >20% between patients with and without PH (p=0.3). The quantitative ILD extent and emphysema extent was also no different between patients with and without PH.

	Whole Cohort	mPAP <25mmHg	mPAP ≥25mmHg	p-value
Number	303	65	238	-
Right heart catheter age	61±11	60±10	61±11	0.6
Gender (%, men)	49	48	50	0.9
BMI (kg/m²)	26.8±6	25.6±5	27.1±6	0.1
Current smoker (%)	23	17	25	0.3
Ex-smoker (%)	36	32	38	0.6
Pack-years	11±14	9±13	11±15	0.3
LTOT prescription (%)	68	39	76	<0.001
Haemodynamics				
mPAP (mmHg)	33±11	19±4	37±9	<0.001
CO (L/m)	4.2±1.3	4.7±1.4	4.1±1.3	0.004
PCWP (mmHg)	10±5	9±5	10±5	0.06
PVR (Wood units)	6.2±4.2	2.5±1.4	7.2±4.1	<0.001
CT metrics				
MPAD (mm)	33.5±5	30.1±5	34.4±4	<0.001
Aorta diameter	31.9±4	30.9±4	32.1±4	0.05
MPAD:Aorta ratio	1.06 [1.0-1.1]	0.9 [0.9-1.1]	1.1 [1.0-1.2]	<0.001
Extent of fibrosis (%,<20%/>20%)	15/85	19/81	13/87	0.3
ILD extent (%)	43±14	44±15	43±14	0.8
Extent of emphysema (%)	3 [0-12]	0 [0-9]	3 [0-12]	0.4

Table 3.5. Demographics, haemodynamics and CT metrics in the whole cohort and stratified by PH status at RHC

Abbreviations: mPAP - mean pulmonary arterial pressure, BMI - body mass index, LTOT - long term oxygen therapy, CO - cardiac output, PCWP - pulmonary capillary wedge pressure, PVR - pulmonary vascular resistance, MPAD - Main pulmonary artery diameter.

3.4.2 Non-Invasive variables in PH and non-PH patients

The mean FEV_1 was 1.6±0.6%; patients with PH had significantly lower FEV_1 (% predicted) than patients without PH (64±20% versus 57±17%, p=0.01) (Table 3.6). The mean FVC (% predicted) was 2.0±0.8%; there was no significant difference between PH and non-PH patients (p=0.4). TLCO and KCO were significantly lower in patients with PH (<0.001 for both). The CPI was no different between patients with and without PH. Patients with PH were significantly more hypoxic than patients without PH, and arterial alveolar gradient

(Aa gradient) was significantly higher in PH patients (<0.001 for both). BNP was significantly higher in patients with PH; 128[54-395]ng/L versus 44[30-72]ng/L (p<0.001). All methods of estimation of pulmonary arterial pressure or RA pressure using echocardiography was significantly higher in patients with PH. Measures of RV morphology and RV function were also significantly worse in patients with PH.

	Whole Cohort	**mPAP <25mmHg**	**mPAP ≥25mmHg**	**p-value**
Number	303	65	238	-
CTD-ILD	107 (35)	29 (45)	78 (33)	0.5
Idiopathic pulmonary fibrosis	72 (24)	19 (29)	53 (22)	0.9
Sarcoid	54 (18)	5 (8)	49 (20)	0.09
Chronic hypersensitivity pneumonitis	26 (9)	10 (15)	16 (7)	0.2
Other ILD	24 (8)	1 (1.5)	23 (10)	0.2
Non-specific interstitial pneumonitis	20 (6)	1 (1.5)	19 (8)	0.4
Pulmonary function tests				
FEV_1	1.6±0.6	1.8±0.7	1.5±0.6	0.001
FEV_1 (% predicted)	58±18	64±20	57±17	0.01
FVC	2.0±0.8	2.1±0.8	2.0±0.8	0.3
FVC (% predicted)	60±20	63±22	60±19	0.3
TLCO (% predicted)	26±10	31±11	24±10	<0.001
KCO (% predicted)	53±17	61±16	50±16	<0.001
CPI	62±11	60±12	63±11	0.01
FVC:TLco ratio	2.6±1.0	2.2±0.7	2.8±1.1	<0.001
PaO_2 (Kpa)	8.0±2.0	9.5±2.0	7.6±1.8	<0.001
Aa gradient (KPa)	5.8±2.7	3.9±1.9	6.5±2.6	<0.001
Brain natriuretic peptide				
BNP (ng/L)	102 [42-265]	44 [30-72]	127 [54-392]	<0.001
Echocardiography				
TRv maximum (m/s)†	3.7±0.7	3.2±0.5	3.9±0.6	<0.001
RVSP (mmHg)	65±21	49±13	70±20	<0.001
RA area (cm^2)	19±8	15±5	20±8	<0.001
RV:LV ratio (diastolic)	0.8±0.4	0.6±0.2	0.9±0.5	<0.001
Pulmonary acceleration time (ms)	77±19	88±20	74±18	<0.001
FAC (%)	37±8	41±7	36±8	<0.001
TAPSE (mm)	18±5	19±5	17±5	0.007

Table 3.6. Non-Invasive variables in PH and non-PH patients

Abbreviations: as per table 3.1 and 3.4. †TRv was available in 92% of the cohort with available echocardiograms.

3.5 Construct validity – Comparison of non-invasive variables between PH severity groups

Non-invasive variables stratified by PH severity are shown in table 3.7. FVC was no different between the PH severity groups (p=0.5). Both gas transfer and gas transfer co-efficient showed a stepwise decrease as PH severity increased. Although patients with mild-moderate PH were not significantly different in terms of gas transfer compared to patients with severe PH (p=0.3). As PH severity increased, the severity of hypoxaemia the Aa gradient and BNP increased. MPAD showed a stepwise increase between PH severities and was significantly different between all groups (p<0.001 for all). ILD severity measured at CT was not different between groups (p=0.3).

Variable	No PH	Mild-Mod PH	Severe PH	P value	No PH vs PH	No PH vs Severe PH	PH vs Severe PH
Number	**65**	**109**	**129**	**-**	**-**	**-**	**-**
CTD-ILD	29 (45)	36 (34)	42 (33)	0.4	-	-	-
IPF	19 (29)	31(28)	22 (16)	0.9	-	-	-
Sarcoid	5 (8)	17 (16)	32 (25)	0.05	0.4	0.01	0.2
CHP	10 (15)	5 (5)	11 (9)	0.3	-	-	-
Other ILD	1 (1.5)	10 (9)	9 (7)	0.9	-	-	-
NSIP	1 (1.5)	9 (8)	13 (10)	0.6	-	-	-
Lung function							
FVC % pred	63±22	59±18	61±20	0.4	-	-	-
TLco % pred	31±11	25±9	23±9	<0.001	<0.001	<0.001	0.3
Kco % pred	61±17	54±16	47±16	<0.001	0.03	<0.001	0.004
PaO_2	9.5±1.9	7.9±1.8	7.3±1.7	<0.001	<0.001	<0.001	0.04
Aa gradient	3.9±1.9	5.9±1.7	7.0±3.1	<0.001	<0.001	<0.001	0.009
Brain natriuretic peptide							
BNP	44 [30-72]	80 [40-157]	232 [102-554]	<0.001	0.003	<0.001	<0.001
CT Variables							
MPAD	30.1±5	33.1±4	35.5±4	<0.001	<0.001	<0.001	<0.001
MPAD:Ao	0.90 [0.9-1.1]	1.00 [1.0-1.1]	1.10 [1.0-1.2]	<0.001	0.005	<0.001	0.02
ILD extent	44±15	44±14	43±14	0.8	-	-	-
Emphysema extent	0 [0-10]	2 [0-11]	4 [0-13]	0.4	-	-	-

Table 3.7. Mean value of non-invasive variables by pulmonary hypertension severity

Abbreviations as per table 3.1 and 3.2. The groups were compared with ANOVA, where a significant difference was found between groups a Tukey HSD comparison was performed for parametric data. Non-parametric data were compared with Kruskal-Wallace and post hoc testing with Wilcoxon signed rank test and Bonferroni correction for multiple testing. Categorical variables were compared with Chi-squared test.

3.6 Discussion

The fact that measures of ILD severity (FVC, CPI and ILD severity measured at CT) did not correlate with invasive haemodynamics corroborates previous work which also found no link between ILD severity measured with FVC (Nathan et al., 2007) or CT (Zisman et al., 2007a). PH occurring due to ILD is not solely due to the overall fibrotic burden of disease or

hypoxia. Measures of the overall efficiency of gaseous exchange correlate moderately with invasive haemodynamics likely due to the overall influence of the pulmonary vascular disease combined with fibrosis. The correlation of FVC/TLco ratio (used in the USA) and KCO appear very similar and it is unlikely that one is superior to the other. The MPAD demonstrated moderate correlation with mPAP in both groups although this appeared stronger in patients with CTD-ILD, sarcoid and NSIP than in IIP, CHP patients. Interestingly, I found no significant correlation between the MPAD:Ao ratio in IIP/CHP patients although a moderate correlation in CTD-ILD, sarcoid and NSIP patients, and mPAP or PVR. I would suggest this is due to demographic differences with IPF patients being more likely to be male and older. The aortic arch has been shown to dilate with increasing age and the presence of hypertension (Craiem et al., 2013, Redheuil et al., 2011). Therefore, this could lessen the utility of the MPAD:aorta ratio in diagnosing ILD associated PH in older patients. As would be expected measures which reflect the effect of increased pulmonary pressure / resistance performed the best in terms of correlation with invasive pressure.

When patients were stratified by PH status, demographics were very similar. BMI was higher in patients with PH 27.1±6Kg/m² versus 25.6±5Kg/m² (although not significantly, p=0.1), which may reflect a higher burden of prednisolone therapy in PH patients. LTOT prescription was also significantly more prevalent in PH patients 75% versus 41% in non-PH patients ($p<0.001$). MPAD measured at CT was significantly larger in PH patients 334.4±4mm versus 0.1±5mm ($p<0.001$), which is compatible with a previous prospective study which showed that MPAD dilatation occurred in patients with ILD-PH (Alhamad et al., 2011). CT extent of disease was no different between patients with and without PH. BNP levels were much

higher in patients with PH 128[54-395]ng/L versus 44[30-72], ($p<0.001$), and all echocardiographic measures of pressure, RV morphology and RV function were significantly worse in PH patients.

When the patients were stratified by PH severity it was clear that patients with severe PH were very different from patients without PH. Although the distinction between patients without PH and mild-moderate PH was less clear. There was a clear decrease in measures of gas exchange in increasing PH severity demonstrating the detrimental impact of worsening PH. A stepwise increase in MPAD and MPAD:Ao was also seen. Again, there was no difference in terms of ILD severity or emphysema extent, to account for the PH.

This analysis highlights that there are important differences between patients with and without PH. It is further evidence that fibrotic burden alone is not the sole cause for PH, and other factors such as genetic susceptibility, rate of lung function decline and acute exacerbations are likely crucial. It supports the idea that identification of patients with PH should be possible by analysis of non-invasive variables.

Chapter 4 Prediction of PH using non-invasive variables

4.1 Rationale

Patients with ILD should undergo regular review with a chest physician to assess symptomology and disease progression. Fundamental to this process is not only a symptom-based review but also functional investigations to help confirm disease stability or progression. This offers not only an opportunity to optimize treatment, but also an ability to screen for associated conditions which may improve: QOL, prognosis or trigger dramatic changes to management such as lung transplant referral. For example, all patients attending clinic should have oxygen saturations checked and where appropriate an assessment for LTOT. Clinic review in ILD is usually at an interval somewhere between 3 months and 6 months. Regular non-invasive investigations are likely to consist of PFT and oxygen saturations at each clinic review, then if disease progression is suspected then further investigations are usually performed (such as CT). As PH occurs commonly in ILD (and is associated with worse outcome) clinical suspicion of its development must be high. If PH is suspected then the next investigation is likely to be an echocardiogram, BNP, and if CT has not been performed recently then is likely that cross sectional imaging is repeated which is often in the form of CT pulmonary angiogram to help exclude co-existent thrombo-embolism. In this chapter of my thesis, I hypothesised that evaluation of these cheap, widely available and safe non-invasive investigations could predict PH in patients with ILD.

4.2 Methods

The cohort previously described was used to evaluate the diagnostic utility of non-invasive investigations. Non-invasive investigations were interrogated if they had been performed within six months of the RHC. Receiver operating characteristic (ROC) were used to evaluate the ability to diagnose PH. Thresholds were selected to maximise both sensitivity and specificity or were based upon recognised PAH international guidelines (Galiè et al., 2015). The strongest candidate variables from the "diagnostic domains" were selected (based on AUC), and included in a model to predict PH. The "diagnostic domains" included:

- Pulmonary function tests
- Echocardiography
- CT
- Biomarker

All patients included in the study to derive a score to predict PH had full baseline investigations performed (e.g. CT, echocardiography, pulmonary function tests (including Aa gradient) and a BNP level within six months of RHC).

4.3 Results

4.3.1 Demographics

The whole cohort was used to evaluate ROC analysis. See chapter 2 and chapter 3 for results of demographics, and non-invasive variables.

4.3.2 Receiver operating characteristics of non-invasive variables ability to predict PH

The following variables had an AUC of greater than 70% for predicting PH (≥25mmHg) at RHC (Table 4.1): TRv (AUC = 79.7%), RVSP (AUC = 80.7%) (where TRv could be measured), RA area (AUC = 73.8%), RV:LV ratio (AUC = 71.5%), Eccentricity Index (AUC = 75.6%), BNP (AUC = 77%), PaO_2 (AUC = 78%), Aa gradient (AUC = 81.7%) and MPAD (AUC = 75.2%). Spirometric and gas transfer performed poorly as discriminators of PH. ILD extent performed very poorly in predicting PH (AUC = 47.9%).

Non-invasive variable	Number (n) with available investigation	Area under the curve (%)
Echocardiography	285	
Tricuspid regurgitation maximum	260	79.7
Right ventricular systolic pressure	260	80.7
Right atrial Area	257	73.8
Right Ventricle to Left Ventricle ratio	219	71.5
Eccentricity index	211	75.6
Fractional area change	243	69.2
Pulmonary acceleration time	254	69.5
TAPSE	246	61.4
Brain natriuretic peptide	278	77
Pulmonary function tests	286	
FEV_1 % predicted	284	60.4
FVC % predicted	284	54.2
TLco % predicted	269	69.6
Kco % predicted	269	67.7
FVC:TLco	269	64.8
Composite physiological index	263	60.5
PaO_2	232	78.0
Alveolar arterial Gradient	232	81.7
CT		
Main pulmonary artery diameter	262	75.2
MPAD:Ao ratio	262	69.2
ILD extent	249	47.9

Table 4.1. Receiver operating curve analysis to predict PH (mPAP ≥25mmHg).

Abbreviations: TAPSE - Trans-annular systolic plane excursion, FEV_1 - Forced expiratory volume in one second, FVC - Forced vital capacity, TLco - Gas transfer, Kco - gas transfer co-efficient, PaO2 - partial pressure of oxygen, MPAD:Ao - Main pulmonary artery to aorta ratio, ILD - Interstitial lung disease.

4.3.3 Demographic and non-invasive investigations

183 patients had a full set of non-invasive baseline investigations available to test the score to predict ILD-PH (Table 4.2). Mean age was 62±11 years, 101 (55.2%) were male. ILD diagnoses included IPF n=55 (30%), CTD-ILD n=50 (27%), sarcoidosis n=35 (19%), NSIP n=12 (7%) and "Other ILD" n= 14 (8%). PH was present in 144 (79%) of the cohort. Non-invasive variables are shown in table 4.2.

Predict ILD-PH Cohort	**(n=183)**
Age	62±11
Gender n, (% male)	101 (55.2)
ILD diagnosis, n (%)	
Idiopathic pulmonary fibrosis	55 (30)
Connective tissue disease	50 (27)
Sarcoidosis	35 (19)
Chronic hypersensitivity pneumonitis	17 (9)
Non-specific interstitial penumonitis	12 (7)
Other ILD	14 (8)
Right heart catheter	
Mean pulmonary artery pressure (mmHg)	33±10
Pulmonary hypertension at RHC, n (%)	144 (79)
Pulmonary vascular resistance (Wood Units)	5.5±3.8
Cardiac Output (L/min/m^2)	4.2±1.3
Pulmonary capillary wedge pressure (mmHg)	10±5
BNP (ng/L)	104[42-266]
Pulmonary function tests	
FEV1 (% predicted)	58±18
FVC (% predicted)	60±19
TLco (% predicted)	25±10
Kco (% predicted)	52±17
Composite physiological index	62±11
Alveolar arterial gradient (kPa)	6.1±2.7
CT scan	
ILD extent (%)	45±14

Table 4.2. Patients with complete non-invasive investigations performed at baseline.

Abbreviations: ILD - Interstitial lung disease, FEV_1 - Forced expiratory volume in one second, FVC - Forced vital capacity, TLco - Gas transfer, Kco - gas transfer co-efficient.

4.4 Performance of the Predict ILD-PH Score

The Predict ILD-PH score is shown in table 4.3. As in ERS/ESC guidelines, TRv is included as intermediate (2.9-3.4m/s), and a high risk (>3.4m/s) (Galie et al., 2016). RA area was also included as per ERS/ESC guidelines, as it is easy to measure in most patients, and when present had a high specificity (87.2%) at discriminating PH (Galie et al., 2016). Aa gradient (>5kPa) was included which had both acceptable sensitivity (75.7%) and specificity (64.1%). BNP was included with its threshold being three times the upper limit of normal at RBH (normal BNP – 20ng/L), and finally a MPAD of >30mm was included (Table 4.3). The ROC curve for the ability of the score to accurately predict PH is shown in figure 4.1.

Non-Invasive investigation	**Threshold**	**Sensitivity (%)**	**Specificity (%)**	**Score**
Tricuspid regurgitation velocity (m/s)	≤2.8 / NA			0
	2.9-3.4			1
	>3.4	71.5	56.4	2
Right Atrial Area (cm^2)	>18	50.0	87.2	3
Alveolar arterial gradient (kPa)	≥5	75.7	64.1	2
Brain Natriuretic Peptide (ng/L)	≥80	66.7	79.5	2
Main pulmonary artery diameter (mm)	>30mm	84.7	46.2	1
Maximum score possible				*10*

Table 4.3. Predict ILD-PH Score.

Abbreviations: NA - Not available. Each non-invasive investigation is shown in addition to the threshold used and the sensitivity and specificity of each threshold. The weighting of each threshold in the ILD-PH score is also shown.

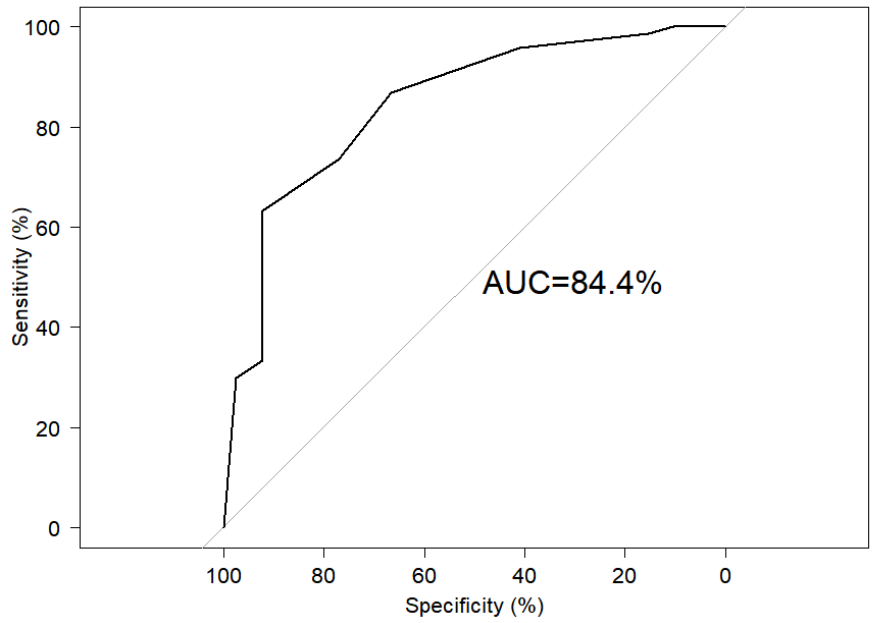


Figure 4.1. Receiver operating characteristics curve for the Predict ILD-PH cohort.

Abbreviations: AUC Area under the curve.

A strong linear correlation was seen between the Predict ILD-PH Score and mPAP at RHC, Spearman's correlation co-efficient = 0.63, p<0.001 (figure 4.2). Using a threshold of 4, the Predict ILD-PH score correctly identified the PH status at RHC in n=151 (82.5%). Patients correctly identified as having PH n=125 (n=144, true positive = 86.8%), and not having PH in n=26 (n=39, true negative = 66.6%). PH status was incorrectly assigned in n=32 (17.5%) of the cohort. n=19 (false negative = 13.2%) were incorrectly thought not to have PH, and n=13 (false positive 33.3%) were thought to have PH when PH was not confirmed at RHC. The overall accuracy (overall probability an individual will be correctly classified) of the Predict ILD-PH score using a threshold of 4 was 82.5% (76.2-87.7%). Table 4.4 and figure 4.3 shows the sensitivity and specificity of scores 1 to 6 using the Predict ILD-PH score.

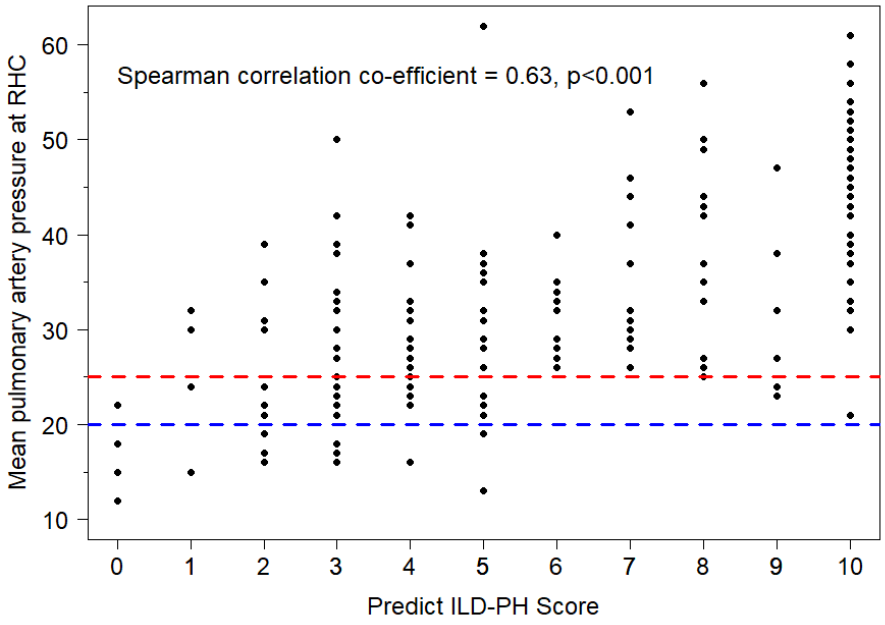


Figure 4.2. Scatter plot demonstrating correlation between the mean pulmonary arterial pressure at RHC and the Predict ILD-PH Score.

The red dashed line demonstrates mean pulmonary artery pressure of 25mmHg at RHC, and the blue dashed line represent patients with elevated pulmonary arterial pressure although not sufficiently elevated to diagnose PH.

Score	Sensitivity	Specificity	PPV	NPV
1	100 (97.5-100)	10.3 (2.9-24.2)	80.5 (78.7-82.1)	100 (-)
2	98.6 (95.1-99.8)	15.4 (5.9-30.5)	81.1 (78.9-83.1)	75 (38.7-93.5)
3	95.8 (91.2-98.5)	41.0 (25.6-57.9)	85.7 (82.2-88.7)	72.7 (52.8-86.4)
4	86.8 (80.2-91.9)	66.7 (49.8-80.9)	90.6 (86.0-93.8)	57.8 (46.0-68.8)
5	73.6 (65.6-80.6)	76.9 (60.7-88.9)	92.2 (86.8-95.5)	44.1 (67.4-80.5)
6	63.2 (54.8-71.1)	92.3 (79.1-98.4)	96.8 (91.0-98.9)	40.5 (35.0-46.2)

Table 4.4. Sensitivity, specificity, positive predictive value and negative predictive value of scores 1 to 6 using the Predict ILD-PH score.

Abbreviations: PPV - Positive predictive value, NPV - Negative predictive value.

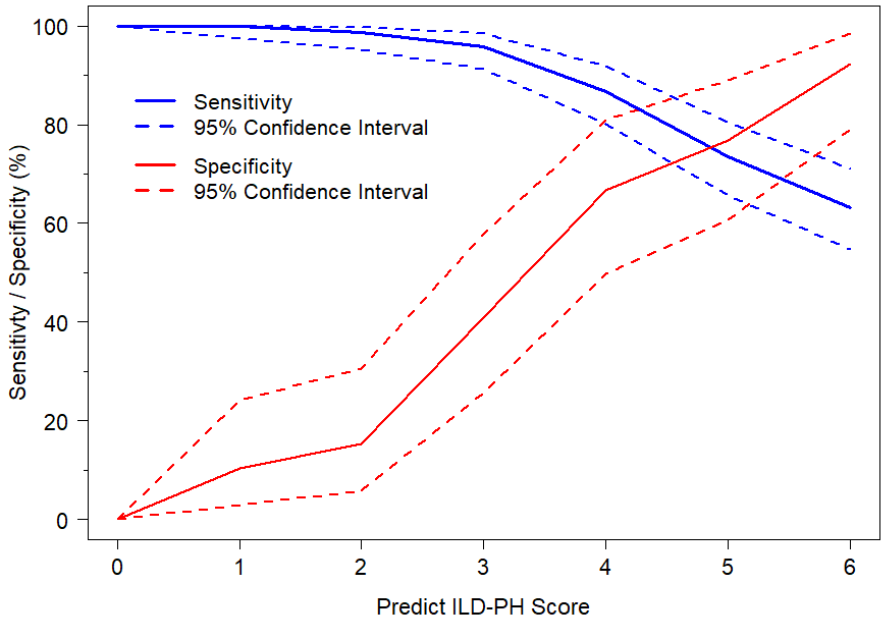


Figure 4.3. Line plot showing sensitivity and specificity of scores 1 to 6 using the Predict ILD-PH score.

4.4.1 Performance of the Predict ILD-PH Score in different ILD diagnostic groups

The Predict ILD-PH score was tested within different ILD diagnostic groups. The Predict ILD-PH score predicted PH with an AUC of 82.8% in patients with IPF / NSIP / CHP and "other" ILD, and an AUC of 86.4% in patients with CTD-ILD / sarcoid. The two receiver operating curves are plotted in figure 4.4.

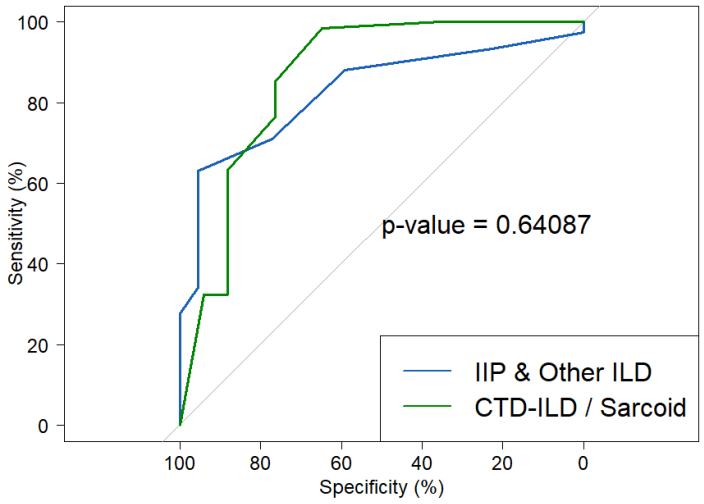


Figure 4.4. Receiver operating curve analysis stratified by ILD diagnosis

Abbreviations: IIP - Idiopathic interstitial pneumonias, ILD - interstitial lung disease, CTD - Connective tissue disease.

4.5 Ability of the Predict ILD-PH Score to predict severe PH

The Predict ILD-PH achieved an AUC of 79.0% in predicting severe PH in the ILD-PH cohort (Severe PH prevalence n= 74, 40.4%). An alternative scoring system to predict severe PH will be discussed in the following chapter.

4.6 Discussion

The predict ILD-PH Score is a multi-modality tool which can predict PH in patients with ILD with reasonable sensitivity and specificity. A score of 4 predicted PH with a sensitivity of 86.8%, and specificity of 66.7%. The score integrates non-invasive tests which are commonly interrogated to refine PH risk stratification, and provides a simple screening tool in patients suspected of having PH. All the variables included within the score can easily be performed in an out-patient setting. The tools strength lies in the fact that many of the thresholds chosen are based on existing expert opinion and other studies. The TRv and RA area threshold was chosen due to its description in the PAH guidelines (Galie et al., 2016). The MPAD threshold was selected in agreement with the work by Chin et al who recently demonstrated that increased pulmonary artery pressure leads to pulmonary artery dilatation and is not related severity of fibrosis or severity of disease at PFT assessment (Chin et al., 2018). They found that MPAD was as accurate for diagnosis of both ILD associated PH and PAH. A MPAD of 30mm gave a sensitivity of 76.3% and specificity of 73.3% in their study (Chin et al., 2018). We had similar findings with a higher sensitivity of 84.7%, and lower specificity of 46.2%. BNP has been evaluated as a diagnostic tool in a cohort similar to ours and combined with other non-invasive variables to predict PH (Ruocco et al., 2015), which is discussed in further detail below. Other studies have also found that a normal BNP is useful in excluding PH in patients with ILD (Andersen et al., 2016). Our results support this finding where a BNP which was three times the upper limit of normal had relatively high specificity for PH.

Although a score of 4 has been chosen as the best balance between sensitivity and specificity many of the patients who were false positives had borderline PH at RHC assessment (figure 4.2). The 13 patients who were false positives using the score had a median mPAP = 22[21-23] mmHg and PVR = 2.8[2.4-4.3] Wood units. Therefore, although these patients did not have PH at RHC they had borderline PH which required careful evaluation. A finding of borderline PH is likely to trigger dramatic changes in management. It is likely that if validated in an external cohort this screening tool could be employed in patients suspected of having IIP associated PH to risk stratify them prior to enrolment to clinical trials.

Previous studies have utilised non-invasive markers to try and predict mPAP at RHC. Zisman et al performed retrospective linear regression studies in 61 patients with IPF undergoing RHC for transplant assessment (Zisman et al., 2007b). An equation using the FVC/TLco ratio and oxygen saturations (SpO_2) breathing room air was created. The model predicted PH with a 71% sensitivity and 81% specificity (PH was present in 32% of the cohort). The model was validated in a separate cohort of 60 IPF patients. Analysis showed that 72% of predicted mPAP was within 5% of the RHC measured mPAP. There was a strong correlation between predicted mPAP and RHC mPAP $r=0.72$, $p<0.001$. The AUC to predict PH were 0.82 and 0.80 depending on which site involved in the study was analysed. They found that if their formula predicted a mPAP of <21mmHg "only 5% of IPF patients with PH (defined as mPAP from RHC ≥25mmHg) will be missed". However, the specificity and PPV were low as only 51% of patients who they suggest for RHC had PH (Zisman et al., 2007b). The authors suggested

that this tool was best employed to rule out PH, rather than rely on it to select individuals to undergo further investigation.

More recently, Alkukhun et al evaluated the ability of the ECG, MPAD, PFT, PaO_2 and 6MWD to predict PH (Alkukhun et al., 2016) in 235 IPF patients undergoing RHC for lung transplant assessment. PH was present in 119 patients (51%). Alkukhun et al found significant differences in non-invasive investigations in patients with and without PH. Although they could not find either a non-invasive test in isolation or in combination which accurately predicted PH at RHC (Alkukhun et al., 2016). Again, the authors found that a combination of non-invasive variables were useful in excluding PH. A MPAD:Ao <1.1, normal ECG QRS axis and normal RV function had a high negative predictive value for PH.

A further study combined non-invasive variables to predict PH. Ruocco et al found that BNP, RVSP, mean pulmonary arterial pressure (PAP) and a TLco level <40% (predicted) had a good discriminative ability to diagnose PH (Ruocco et al., 2015). They suggested an algorithm consisting of: RVSP≥40mmHg, mean PAP ≥25mmHg, TAPSE ≤16mm, BNP >50pg/ml and TLco <40%, with each parameter being awarded one point. In 37 patients with invasive data available they found that a score of ≥3 predicted PH with a concordance index of 0.96, and Cohen's "K" index of 0.825. There were no patients with a score of 3 or more who did not have PH. The authors suggest that an algorithm including BNP, TLco and echocardiography could be useful for non-invasive screening of PH occurring in ILD. I tested this algorithm in our cohort although it was not possible to use the same BNP threshold due to differing units although replaced their BNP threshold with our own threshold. Overall the Functional Lung test, Echocardiographic and BNP assessment (FLEB) so named by Ruocco (Ruocco et al.,

2015) et al achieved an AUC in our ILD-PH cohort of 75.7% (data not shown). A threshold of 3 achieved a sensitivity of 68.4% and specificity of 72.5, which had an overall accuracy of 69.2% (62.2-75.6%). I believe these studies provide complimentary conclusions. It is highly likely that cohort differences are in part responsible for the different findings although additionally Ruocco's cohort only had RHC data available in 37 patients, whereas all our patients had RHC. Nevertheless, both our studies agree that non-invasive assessment of PH is possible, and the integration of multiple non-invasive investigations is more useful than relying on investigations in isolation.

4.7 Limitations

The cohort requires careful consideration when analysing the usefulness of the diagnostic tool in which it was created. The data is retrospective and from a single institution which inherently introduces bias which I sought to minimize by examining consecutive patients. This cohort of patients had already proven themselves to be a very high risk of PH as they had undergone the invasive test to confirm its presence. Therefore, PH prevalence was extremely high. It is likely that the threshold which offers the best combination of sensitivity and specificity to detect PH will vary according to PH prevalence. If this screening tool was applied to cohorts with a much lower prevalence of PH, then it is likely the best threshold to diagnose PH (and indeed the weighting of each threshold) would change. Therefore, the Predict ILD-PH tool is only valid in patients with fibrotic ILD where clinical suspicion of PH is high. The tool requires validation ideally in a prospective external cohort prior to it being employed as a diagnostic tool in everyday practice. Unfortunately, due to a lack of useful

6MWD being stored on the PH database the usefulness of 6MWD, desaturation and heart rate variability could not be interpreted.

4.8 Conclusions

The Predict ILD-PH Score integrates common, easily available non-invasive investigations to refine PH prediction in patients who have clinically suspected ILD-PH. A score of 4 or above predicted PH with a sensitivity of 86.8%, and specificity of 66.7%, and an overall accuracy of 82.5%. This tool could prove useful in evaluation for clinical trials to evaluate pulmonary vasodilators in ILD-PH.

Chapter 5, Prediction of severe PH in ILD patients

5.1 Rationale for study

The current ERS/ESC guidelines recommend that ILD patients with severe PH (mPAP >35mmHg at RHC) should undergo specialist evaluation at centres with experience in both ILD and PH (Galie et al., 2016). Additional investigation to exclude co-existent disease should be performed. Patients should be considered for PH therapies or enrolment into clinical trials in ILD-PH. The major difficulty with identifying patients for further evaluation is reliable identification of patients with severe PH. The major screening tool for PH is echocardiography, although in ILD previous studies have shown significant limitations in detecting the presence or determining the severity of PH. For example, Arcasoy et al demonstrated that RVSP estimation was only possible in 44% of patients with advanced lung disease (28% of which had ILD), and 48% of patients were misclassified as having PH (Arcasoy et al., 2003). Another significant difficulty with screening tests remains the choice of threshold. Nathan et al evaluated 110 IPF patients, where TRv was seen in 54.5% of the cohort, and PH occurred in 32% of the individuals where no TRv was measurable. An adequate threshold RVSP which predicted PH could not be demonstrated (Nathan et al., 2008b). In determining the probability of PH, ERS/ESC guidelines suggest that although TRv is important, additional echocardiographic components are needed to offer complimentary information, particularly when TRv is either borderline or not available. These include RV:LV basal size ratio, flattening of the interventricular septum (equivalent to LV eccentricity index), pulmonary acceleration time, mean pulmonary pressure derived from the early

diastolic pulmonary regurgitation velocity, and RA area (Galie et al., 2016). RV FAC is an early marker of radial RV dysfunction and a useful parameter used in PAH (Rudski et al., 2010, da Costa Junior et al., 2016).

I hypothesized that patients with severe PH would have significant differences in terms of echocardiographic evaluation, and that an echocardiographic score utilising measures of raised pulmonary arterial pressure and RV function could reliably identify patients with severe PH associated ILD-PH.

5.2 Methods

5.2.1 Patient selection

Patients were selected for the study from the ILD-PH cohort previously described in chapter 2. Patients were eligible for the study if they had an echocardiogram within six months of the initial diagnostic RHC. Derivation and validation cohorts were created. The score was derived and tested within the derivation cohort and tested separately in the validation cohort. To ensure a well described derivation cohort, patients were included if they had a full set of investigations within six months of RHC including; echocardiography, BNP and PFT. Patients selected for the validation cohort had one of the following investigations missing either BNP or PFT.

5.2.2 Generation of the stepwise echocardiographic score

Potential echocardiographic variables and thresholds of each variable were selected following an expert panel review and according to ERS/ESC guidelines a priori. Variables were combined into a contingent stepwise model if their AUC was >70%. This was to create a pragmatic scoring system, to allow for missing echocardiographic data as often occurs in

ILD patients. When the strongest predictor of severe PH was present and positive then no further analysis was necessary. Otherwise the score was designed to be run through its entirety until either it becomes positive or severe PH is not thought to be present. The weighting of each threshold within the score was determined by completing 900,000 different score combinations and the model with the highest AUC was chosen (Figure 5.1). The threshold for the score becoming positive and severe PH likely was chosen to maximise both sensitivity and specificity.

A post-hoc analysis was performed in the whole cohort (derivation and validation cohorts combined) to blind available RVSP to levels seen in historic cohorts (removing available data). This was performed to check the score remained valid with increasing un-availability of RVSP. A bootstrapping method which randomly blinded RVSP at each percentage point from 8% missing RVSP values (as was found in our cohort) up to 60% which was found in historic cohorts (Arcasoy et al., 2003, Nathan et al., 2008b) was performed. One hundred iterations were performed at each percentage point missing RVSP data between 8 and 60%, with patients selected at random for each iteration. The sensitivity and specificity of the score was compared to using RVSP alone with the same method.

Finally, the prognostic ability of the stepwise echocardiographic scores was evaluated with cox regression analysis and survival estimated using Kaplan-Meier curves. The start of follow up was from the date of the echocardiogram and outcome was defined as death or lung transplant. Patients were censored at their last clinical contact if they remained alive at the end of the study.

5.3 Results

5.3.1 Patient demographics and ILD diagnosis

The derivation cohort was made up of 210 patients (Table 5.1). Mean age was 61±11 years, n=115 were male (55%). ILD diagnoses included IPF n= 62 (29%), CTD-ILD n= 59 (28%), sarcoidosis n= 43 (20%), CHP n= 16 (8%), NSIP n=16 (8%) and "other ILDs" n= 14 (7%). CTD-ILD patients were made up of patients with scleroderma (36%), undifferentiated CTD (14%), RA (14%), antisynthetase syndrome (14%), mixed CTD (12%), Sjogren's syndrome (5%) and SLE (5%).

5.3.2 Right heart catheterisation and BNP data

PH was present in n= 164 (78.0%) of the cohort which was mild-moderate (mPAP ≥25mmHg and <35mmHg) in n= 79 (37.6%), and severe (mPAP ≥35mmHg) in n= 85 (40.4%) (Table 5.1). As expected, both PVR and BNP showed a step wise increase with increasing severity of mPAP. Patients with severe PH were younger than patients with mild-moderate PH ($p<0.001$). Patients with sarcoidosis were more likely to have severe PH (n=25, 58%) versus (n=60, 36%) in the non-sarcoid group (p=0.01).

5.3.3 Lung function and severity of fibrosis at CT analysis

Spirometric parameters showed no significant differences between PH severity groups (Table 5.1). However, there was a stepwise deterioration in Kco, and PaO_2 as PH increased in severity ($p<0.001$). ILD extent was > 20% extent in 86% of the cohort and there were no significant differences in ILD severity between groups (p=0.2).

	Derivation cohort (n=210)	mPAP <25mmHg (n=46)	mPAP 25-34mmHg (n=79)	mPAP ≥35mmHg (n=85)	p value
Age, years	61±11	63±11	64±11	58±12	0.004
Gender, % male	55	52	54	56	0.9
ILD diagnosis, n (%)					
CTD	59 (28)	15 (25)	21 (36)	23 (39)	0.7
Sarcoidosis	43 (20)	4 (9)	14 (33)	25 (58)	0.01
IPF	62 (29)	18 (29)	28 (45)	16 (26)	0.02
CHP	16 (8)	6 (38)	2 (12)	8 (50)	0.1
NSIP	16 (8)	2 (12)	8 (50)	6 (38)	0.5
Other ILD	14 (7)	1 (7)	6 (43)	7 (50)	0.4
Right heart catheter					
mPAP (mmHg)	33±11	20±4	29±3	43±7	<0.001
PVR (Wood Units)	6.0±3.6	2.6±1.5	4.6±1.8	8.8±3.8	<0.001
CO (L/min/m^2)	4.3±1.3	4.8±1.3	4.1±1.3	4.1±1.2	0.02
PCWP (mmHg)	10±5	8±5	10±5	11±5	0.008
BNP (ng/L)	102[44-266]	48[30-72]	90[42-141]	241[105-436]	<0.001
Pulmonary function tests					
FEV1 (litres)	1.6±0.6	1.6±0.6	1.5±0.5	1.6±0.6	0.9
FEV1 (% predicted)	58±18	62±21	57±17	57±17	0.2
FVC (litres)	2.0±0.8	2.0±0.8	1.9±0.7	2.2±0.9	0.2
FVC (% predicted)	60±20	61±22	59 ±18	62±22	0.7
TLco (% predicted)	25±10	28±10	25±9	24 ±10	0.04
Kco (% predicted)	52±17	59±18	54±16	48±16	<0.001
PaO_2 (kPa)	7.9±1.9	8.9±1.9	8.1±1.9	7.1±1.7	<0.001
CT scan					
ILD extent (<20%/>20%)	14/86	15/85	19/81	9/91	0.2

Table 5.1. Right heart catheter and non-invasive variables.

Abbreviations: ILD - interstitial lung disease, CTD - connective tissue disease, IPF - idiopathic pulmonary fibrosis, CHP - chronic hypersensitivity pneumonitis, NSIP - non-specific interstitial pneumonia, mPAP - mean pulmonary pressure at right heart catheterisation, PVR - pulmonary vascular resistance, CO - cardiac output, PCWP - pulmonary capillary wedge pressure, BNP - brain natriuretic peptide, FEV1 - Forced expiratory volume in one second, FVC - forced vital capacity, TLCO - transfer factor, KCO - transfer coefficient, PaO2 - arterial oxygen content (by capillary blood gas analysis), CT - computed tomography. Data are mean±SD or median [interquartile range]. Data compared with ANOVA or Kruskal-Wallace test as appropriate.

5.3.4 Echocardiographic results

TRv was detectable in 92% of studies (Table 5.2). Interestingly TRv was most likely to be unavailable in individuals with an ILD diagnosis of sarcoidosis with 19% of patients having

inadequate TRv doppler traces versus only 5% in the remainder of the cohort (p=0.002). Echocardiographic data was widely available in the cohort although mPAP derived from early pulmonary regurgitation velocity was only available in 20% of studies. All measures of pressure, morphology and function showed a stepwise deterioration with increasing PH severity (Table 5.2).

	Availability (%)	Derivation cohort, total (n=228)	mPAP <25mmHg (n=46)	mPAP 25-34 mmHg (n=79)	mPAP ≥35mmHg (n=85)	p value
TRmax velocity (m/sec)	92	3.7±0.6	3.3±0.5	3.6±0.5	4.0±0.6	<0.001
RVSP (mmHg)	92	66±19	53±13	61±18	76±17	<0.001
Pulmonary acceleration time (ms)	93	77±18	82±17	80±19	70±14	<0.001
Systolic eccentricity index	82	1.4±0.4	1.1±0.2	1.2±0.3	1.6±0.5	<0.001
Early PR velocity (m/sec)	20	2.5±0.5	2.0±0.3	2.3±0.5	2.7±0.4	0.001
RA Pressure (mmHg)	99.5	5[5-10]	5[5-10]	5[5-10]	10[5-10]	0.008
Fractional area change (%)	93	37±8	41±8	39±7	34±8	<0.001
Right atrial area (cm^2)	93	20±8	15±4	18±6	24±8	<0.001
TAPSE (cm)	92	1.8±0.5	1.9±0.4	1.9±0.5	1.7±0.4	<0.001
RV:LV short axis dimension ratio (systolic)	81	0.9[0.7-1.4]	0.7[0.6-0.9]	1.0[0.6-1.1]	1.3[0.9-2.0]	<0.001

Table 5.2. Echocardiographic variables stratified by PH severity.

Abbreviations: TR - Tricuspid regurgitant, mPAP mean pulmonary pressure, RVSP - right ventricular systolic pressure, PR - pulmonary regurgitation, RA - right atrial, TAPSE - Tricuspid annular plane systolic excursion, RV - right ventricular, LV - left ventricular. Data are mean±SD or median [interquartile range]. Data compared with ANOVA or Kruskal-Wallace test as appropriate.

5.3.5 The stepwise echocardiographic score

The strongest predictors of severe PH were; RVSP (AUC 80.1%), early pulmonary regurgitation gradient velocity (*adding* RA pressure, AUC 80.7%; *without* RA pressure, AUC 80.8%), RA area (AUC 75.5%), TRv (AUC 77.1%), systolic RV:LV diameter on short axis view

(AUC 77.5%), LV eccentricity index (AUC 80.6%), and RV FAC (AUC 72%) (Figure 5.2). Other echocardiographic variables performed less well in PH discrimination including; TAPSE (68.1%), pulmonary acceleration time (AUC 66.1%), RA pressure (AUC 62.4%) and myocardial systolic velocity (AUC 65.2%). The generation of the optimal score for each threshold is shown in figure 5.1.

Right ventricular systolic pressure (mmHg)	min	max	Permutations	Score
> 64	4	8	5	7
>35	1	5	5	1
≤ 35 or not available	0	0	1	0
Right atrial area (cm^2)	**min**	**max**	**Permutations**	**Score**
> 25	3	7	5	6
> 20	1	2	4	1
≤ 20 or not available	0	0	1	0
Early diastolic pulmonary regurgitation velocity (mmHg)	**min**	**max**	**Permutations**	**Score**
> 36	4	8	5	4
≥20	1	3	3	3
<20 or not available	0	0	1	0
RV fractional area change (%)	**min**	**max**	**Permutations**	**Score**
< 35	1	5	5	4
≥ 35	0	0	1	0
RV / LV short axis dimension	**min**	**max**	**Permutations**	**Score**
> 1	1	6	6	3
≤ 1 or not available	0	0	0	0
Systolic eccentricity Index	**min**	**max**	**Permutations**	**Score**
≥ 1.1	1	4	4	1
< 1.1 or not available	0	0	1	0
			Total number of permutations	**Maximum Score**
			900,000	25

Figure 5.1. Threshold values of each individual variables within the stepwise echocardiographic score

All individual components within the stepwise echocardiographic score had an AUC >70% to predict severe PH (mPAP ≥35mmHg). The thresholds for each variable were chosen a priori based upon expert opinion and guidelines. The weighting of each threshold within the score was then determined by running a loop analysis of 900 000 different score combinations. Each variable had a minimum and maximum weighting within the score determined by expert opinion. The model with the highest AUC was chosen. The final column shows the stepwise echocardiographic weighting of each threshold and the maximum score.

The following were integrated into a stepwise score to predict PH; RVSP, RA area, early pulmonary regurgitation gradient velocity, FAC, RV:LV ratio and eccentricity index (Figure 5.2).

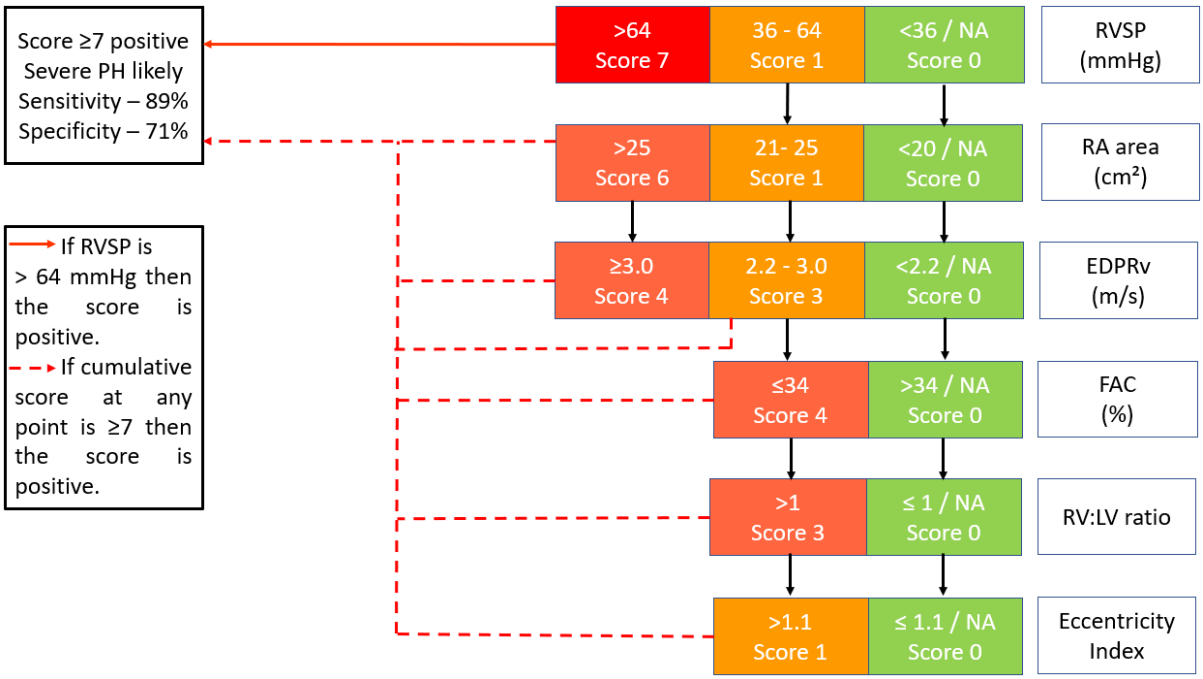


Figure 5.2. Stepwise echocardiographic score to predict severe PH associated with ILD.

Abbreviations: RVSP - Right ventricular systolic pressure, RA - Right atrial, EDPRv - Early diastolic pulmonary regurgitation velocity, FAC - Fractional area change, RV - Right ventricle, LV - Left ventricle. If an overall score of ≥7 is achieved, then the stepwise echocardiographic score is positive, and no further analysis is necessary. A positive result can be achieved at the first step if RVSP is >64mmHg. If the RVSP is <65 or not present, then the score is designed to be worked through all steps until either a score of 7 is achieved or the stepwise echocardiographic score is negative.

A stepwise echocardiographic score of ≥7 was chosen as the best balance between sensitivity 89% and specificity 71%. The PPV was 68%, and NPV 90%. Despite six steps in stepwise score, 88% of the cohort were positive by the first step due to a RVSP >64mmHg. A

further 5% of patients were positive on step 2 meaning that 93% of the cohort was positive by the second step.

The stepwise echocardiographic score correctly assigned PH status in 78% of the cohort. Severe PH was missed in just 5% of the cohort (false negatives), and 17% of the cohort were incorrectly thought to have severe PH (false positives).

5.3.6 The stepwise echocardiographic score in different ILD diagnostic groups

The ability of the score was reanalysed with each of the largest diagnostic groups (IPF, CTD-ILD, sarcoid) removed from the cohort (figure 5.3). The AUC were very similar with each ILD group removed in turn; IPF excluded (AUC 83.9%), CTD-ILD excluded (AUC 84.3%) and sarcoid excluded (AUC 85.6%).

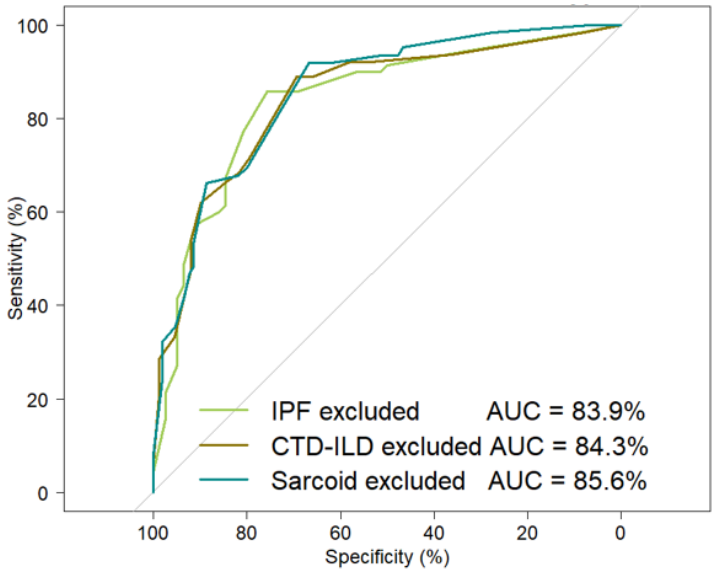


Figure 5.3.Receiver operator curve analysis with each of the largest ILD subtypes excluded

Abbreviations: IPF - Idiopathic pulmonary fibrosis, CTD - Connective tissue disease, ILD - Interstitial lung disease.

5.3.7 Performance of the stepwise echocardiographic score in the Validation cohort

Comparison of the validation and derivation cohort is performed in table 5.3. Patients were the same age as in the derivation cohort, although there were fewer males (39% versus 55%, p=0.03). This was due to more patients with CTD-ILD (54% in validation versus 28% in derivation, p<0.001, who are more likely to be female) and fewer patients with IPF (8% in validation versus 29% in derivation, p=0.007, who are more likely to be male). Otherwise haemodynamics, BNP, PFT's and ILD severity of fibrosis was not different. The stepwise echocardiographic score performed similarly in the validation cohort. The AUC in the derivation cohort was 84.8% versus 83.1% in the validation cohort, p=0.8.

	Derivation Cohort (n=210)	**Validation Cohort** (n=61)	p value
Age, year	61±11	61±13	0.9
Gender, % male	55	39	0.03
ILD diagnosis (n/%)			
CTD	59 (28)	33 (54)	<0.001
Sarcoidosis	43 (20)	6 (10)	0.06
IPF	62 (29)	5 (8)	0.007
CHP	16 (8)	6 (10)	0.5
NSIP	16 (8)	6 (10)	0.5
Other ILD	14 (7)	5 (8)	0.7
Right heart catheter			
mPAP (mmHg)	33±11	33±12	0.8
PVR (Wood units)	6.0±3.6	6.9±5.6	0.3
CO (litres/min)	4.3±1.3	4.1±1.4	0.6
PCWP (mmHg)	10±5	10±5	0.9
BNP (ng/L)	102[44-266]	103[42-306]	0.7
Pulmonary function tests			
FEV1 (litres)	1.6±0.6	1.6±0.8	0.5
FEV1 (% predicted)	58±18	62±21	0.3
FVC (litres)	2.0±0.8	2.0±0.9	0.7
FVC (% predicted)	60±20	65±22	0.2
TLco (%predicted)	25±10	27±10	0.2
Kco (%predicted)	52±17	54±17	0.7
PaO_2 (kPa)	7.9±1.9	8.5±2.1	0.1
CT scan			
ILD extent (<20%/>20%)	14/86	19/81	0.5

Table 5.3. Right heart catheter and non-invasive variables compared between the derivation and validation cohort

Abbreviations As per table 5.1 Data are mean±SD or median [interquartile range]. Data compared with T-test or Wilcoxon Rank-Sum test as appropriate.

5.3.8 Performance of the stepwise echocardiographic score when RVSP was unavailable

The derivation and validation cohort were combined to evaluate the impact of increasing RVSP unavailability as has been seen in historic cohorts. The prevalence of unavailable RVSP was increased from 8% (as was seen in our cohort) to 60% unavailable RVSP (figure 5.4, panel A). The AUC dropped from 84% seen in the original cohort to 79% when 60% of RVSP

was unavailable to analysis. The effect of relying on TRv alone was modelled against using the stepwise echocardiographic score. There was a dramatic reduction in sensitivity when TRv alone was relied upon when it became increasingly unavailable. However, the sensitivity of the composite echocardiographic score was relatively well preserved (figure 5.4, panel B).

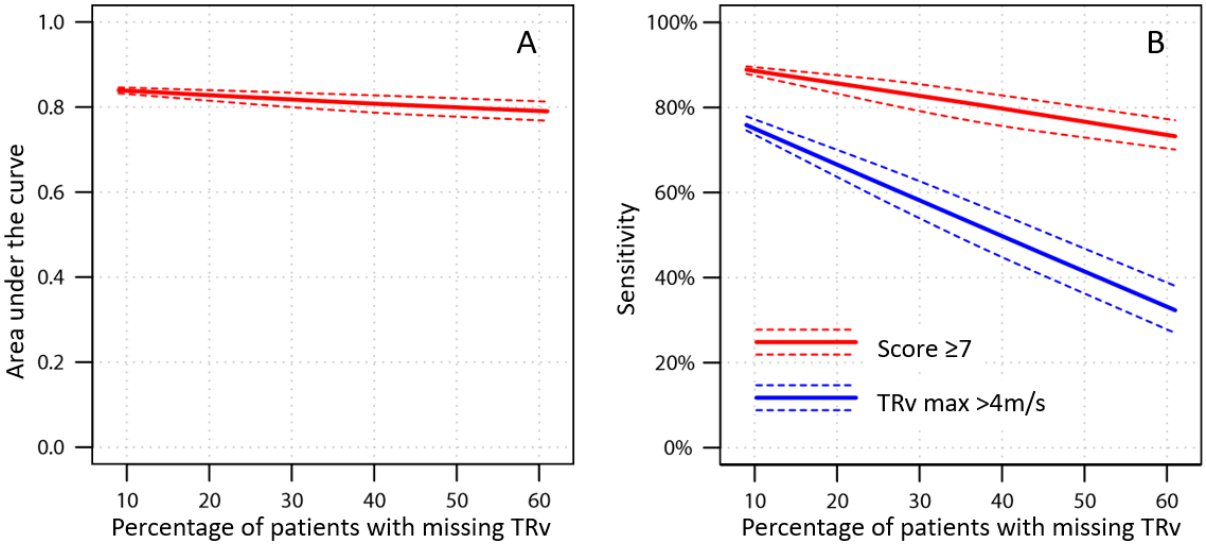


Figure 5.4. Line plots demonstrating the effect of increasing unavailability of right ventricular systolic pressure on the area under the curve (AUC) to predict severe PH

Abbreviations: TRv max – Tricuspid regurgitation velocity. (Panel A), The effect on sensitivity of increasing TRv unavailability is shown using the echocardiographic score and by relying on TRv in isolation (Panel B). TRv unavailability was simulated by randomly blinding available TRv values. This was performed using bootstrapping (100 iterations at each 1% point from 8% missing to 60% missing TRv) and the AUC and sensitivity was calculated at each iteration of blinded data. Plot A shows that the AUC of the stepwise echocardiographic score is very well preserved despite increasing TRv unavailability. Plot B shows that there was only a minor reduction in the sensitivity of the stepwise echocardiographic score whereas the sensitivity of relying on TRv more than halved.

5.3.9 Prognostic importance of a positive stepwise echocardiographic score

Median follow up in the study was 2.50[1.05-3.16] years. n = 205 patients (75.6%) died and n = 12 (5%) of patients underwent lung transplant. A positive composite echocardiographic score was associated with an adverse outcome (HR:1.43, CI:1.09-1.87, p=0.01) (figure 5.5).

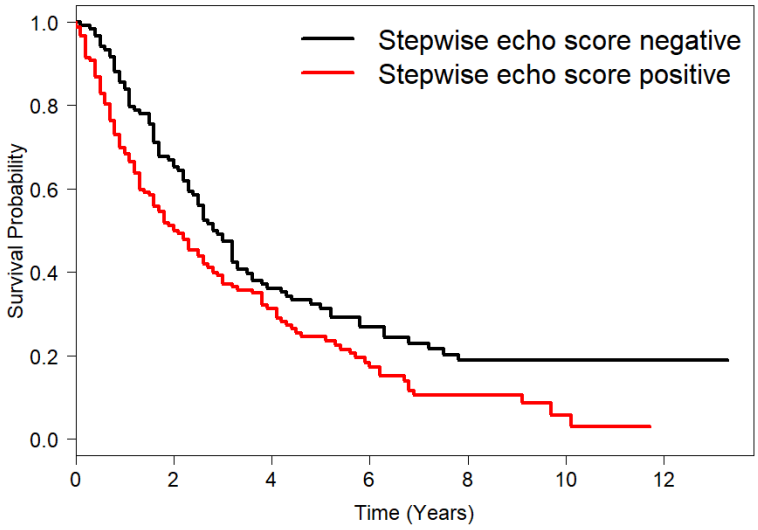


Figure 5.5. Kaplan-Meier plot demonstrating adverse outcome associated with a positive stepwise echocardiographic score.

Patients stratified by stepwise echocardiographic score <7 (black line, n= 119), and ≥7 (red line, n=152), Hazard ratio = 1.43, confidence interval = 1.09-1.87, p=0.01.

5.4 Discussion

This is the first validated score using non-invasive echocardiographic assessment combining traditional assessment of RVSP and additional PH variables to identify severe PH in ILD. The stepwise echocardiographic score predicted severe PH with a sensitivity of 89% and specificity of 71%. The stepwise echocardiographic score correctly assigned PH status in 78% of the cohort and had only 5% of false negatives. Furthermore, the diagnostic utility of the

score was preserved even when the most powerful predictor was blinded in up to 60% of the cohort.

The stepwise echocardiographic score shows when RVSP is present in a patient with suspected ILD-PH and is >64mmHg then severe PH is extremely likely. This simple step was responsible for 88% of our patients achieving a positive stepwise echocardiographic score. The additional steps are required to ensure that severe PH in individuals without RVSP measurements is not missed. The application of this finding is extremely important for any individual who is undergoing echocardiographic assessment for suspected ILD-PH and should trigger referral to expert PH and ILD services. ILD physicians are acutely aware of the fallibility of echocardiographic screening in their patient population, and this study provides further guidance on which additional PH signs are the most important if TRv is not available. I acknowledge that the high RVSP availability is in part due to referral bias, so we ensured the score was resilient to increasing unavailability of TRv.

The ILD cohort in which the score was derived and tested had a very broad range of both idiopathic interstitial pneumonias as well as CTD-ILD, sarcoidosis and CHP. Therefore, the stepwise echocardiographic score is applicable in a broad range of ILD patients. I ensured that the score was not overly influenced by any one of the large diagnostic groups by excluding them and retesting the score and it showed minimal change. I also demonstrated that although the ILD diagnosis distribution in the validation cohort was slightly different to the derivation cohort (more CTD-ILD and less IPF patients) the score performed as well.

This stepwise echocardiographic score could play a role in selecting patients to undergo RHC as per the ERS/ESC guidelines (Galie et al., 2016). RHC is increasingly not being performed in

IIP, CHP and idiopathic NSIP patients. RHC tends to be reserved to those where accurate prognostic assessment is essential including where PH severity appears out of proportion to the underlying ILD and in patients being worked up for transplant. This stepwise echocardiographic score has a role in screening high-risk individuals for onward referral to specialist units and subsequent RHC.

A recent echocardiographic study (Amsallem et al., 2017) evaluated right heart measurements for detection of PH in 192 patients with advanced lung disease (ALD) (56% of which had an ILD). This demonstrated that when matched to controls patients with ALD without PH have significantly larger RV dimensions and worse systolic function than healthy controls. The authors found that when TRv was present the integration of other right heart abnormalities did not add to discrimination of PH (using a mPAP ≥25mmHg). However, the presence of two or more abnormal right heart measures in patients without a TRv (of which 47% had PH) did discriminate between patients with and without PH, and the authors suggest that discrimination is greater when PH is severe (Amsallem et al., 2017). Our study clearly supports and extends these findings with just 12% of our false positives having a mPAP of less than 25mmHg at RHC.

What is intriguing is why do patients who do not have PH at RHC assessment have either extremely high pressure at echocardiographic assessment or other signs of PH. This is not unique to our cohort; Alkukhun et al found that 22 of 88 (25%) IPF patients without PH at RHC had some degree of RV dysfunction (Alkukhun et al., 2016), and in a echocardiographic study (where PH was defined by echocardiography rather by RHC), compared to age and sex matched controls, patients with IPF without PH had features of impaired diastolic and

systolic RV function (D'Andrea et al., 2016). In COPD, Hilde et al. demonstrated that RV impairment and increased RV wall thickness were present even in patients with mPAP 18±3mmHg at RHC (Hilde et al., 2013) suggesting RV hypertrophy occurs before PH is established. Co-existent obstructive lung disease is not un-common in ILD patients (particularly IPF and sarcoidosis), and it is likely a similar process occurs in ILD patients. Some potential mechanisms contributing to this in ILD (without the development of PH) include; Increased RV afterload due to loss of the pulmonary capillary bed and alveolar hypoxaemia from the fibrotic process; and reduced RV preload due to a loss of lung elasticity and stiffer intrathoracic structures (Sietsema, 2001). Another uncertainty is the prognosis of these patients who show signs of RV dysfunction (when assessed by echocardiography), presumably their prognosis is better than patients with PH, but worse than patients without RV dysfunction and PH. It is possible that some of the patients who demonstrated elevated pressures / RV dysfunction at echocardiogram (with no PH at RHC) recently underwent an exacerbation which had improved by the RHC. Additionally, echocardiographic and RHC measurements are obtained at rest, rather than during or following physical exertion. It is probable that during times of exertion / exacerbation RVSP increases and RV function is more deleteriously affected. It is probable that the patients with borderline pressures at RHC manifest PH and RV dysfunction with exercise / exacerbation.

5.5 Limitations

The limitations discussed in the previous chapter also apply in this chapter, although due to the lower prevalence of severe PH versus PH in general it is likely that some of the bias has

been negated. The major confounder in this study is the fact that much of the ILD-PH cohort were referred because of both a clinical suspicion of PH and echocardiographic signs of PH. The reason for referral was known in 85% of the cohort, 88% of which were referred directly because of signs of PH on echocardiography. This in part explains the high TRv availability in our cohort. Although it is also likely that, as RBH is a cardiac centre of excellence, that the increased expertise will positively influence the ability of detecting TRv. Another factor is the high prevalence of patients with severe PH in our population (40.4%); when pressure is grossly elevated it is easier to measure the TRv. However, we sought to minimize these issues by modelling the increased unavailability of TRv such that has been seen in more historic cohorts to ensure the score retained diagnostic ability.

We included patients with CTD-ILD and sarcoidosis within the cohort so that the score could be directly applicable to them. As patients with CTD-ILD and sarcoidosis can develop PH independent of ILD this could be interpreted as a weakness. However, care was taken to ensure that all patients had ILD, with all CT's being checked for severity of ILD. Furthermore, analysing the score with the individual groups removed did not affect the diagnostic utility of the score.

5.6 Conclusion

In suspected ILD-PH when RVSP is present and is >64mmHg, severe PH is very likely. If clinical suspicion of severe PH is high but RVSP is either not present or <64mmHg then the stepwise ILD PH score can be used.

Chapter 6, Predictive and prognostic role of CT Pulmonary Angiography in suspected ILD-PH

6.1 Rationale for the study

CTPA is often utilised by ILD physicians in patients who have deteriorated; especially where there has been a deterioration in gas transfer and stability in the FVC, to help exclude a pulmonary embolism. CTPA offers an opportunity to risk stratify and to help refine decisions regarding referral to PH services. The development of RV dilatation occurs late in PAH (Naeije and Manes, 2014) and therefore its presence on a CTPA should prompt evaluation for PH. Radiologists often comment on right ventricular dimensions, and other ancillary findings at CTPA. Although there is a strong evidence base in acute pulmonary embolism (PE) that RV dilatation is an adverse prognostic sign, the significance of RV dilatation at CTPA in suspected ILD-PH is not known. Unlike in thromboembolic disease where obstructive thrombus normally resolves, ILD usually progresses and therefore the presence of RV dilatation should imply a worse prognosis. We performed this study to evaluate the predictive and prognostic abilities of CTPA measurements in patients suspected of having ILD-PH.

6.1.2 Hypothesis

I hypothesized that an increased RV:LV diameter and other ancillary findings on CTPA in patients with ILD would predict PH and patients with a dilated RV would have a worse prognosis.

6.2 Methods

Patients were identified from the ILD-PH cohort as previously described in chapter 2. Patients were included in the study if a CTPA was performed within six months of their baseline RHC. Patients with thromboembolic disease (segmental or sub-segmental) or suspected chronic thromboembolic PH at CTPA were excluded.

6.2.1 CTPA acquisition and measurements

All CTPA examinations were performed at the discretion of the clinical team at the time of the PH assessment. CT was performed at full inspiration. Intravenous administration of contrast medium was performed with standard intravenous access, using automated administrator injection equipment. Bolus tracking was used to trigger the start of the acquisition of images. ECG gating of image acquisition was not performed, and no reconstruction of images was performed. See Methods chapter section 2.2.4 for methodology of CTPA measurements performed. ILD severity was scored as per section 2.2.2 of the methods section.

6.2.2 Statistical analysis

Correlation of CT measured RV:LV with other variables was performed with Spearman's correlation. Strength of correlation (r) was defined as follows: >0.5, large, 0.5 – 0.3, moderate 0.3 – 0.1 small and <0.1 trivial. Continuous variables were compared between PH severity groups (No PH <25mmHg, mild to moderate PH 25-34mmHg and severe PH ≥35mmHg) using analysis of variance or Kruskall-Wallace, as appropriate. For categorical variables chi-squared test was used. Where a significant difference amongst the groups was demonstarted, post hoc testing was performed with Tukey honest significant difference

test, or Wilcoxon rank sum test with Bonferroni adjustment to account for multiple testing. Receiver operator curve analysis (ROC) was used for continuous variables ability to predict PH at RHC and the threshold to predict PH evaluated using logistic regression and sensitivity and specificity analysis. Survival analysis was performed using Cox-proportional hazard modeling, with the date of the CTPA as the start of follow up. The primary end-point was if either death or lung transplant occurred, and all other patients were censored at the last date of clincial contact. For multivariable selection backward selection was used; the multivariable model included: age, severity of fibrosis measured at CT, a diagnosis of IPF, and the RV:LV*largest* ratio.

A subset of the cohort (n=60) was analysed by a Thoracic radiologist (RA with 20 years' experience), and CTPA measurments performed independantly. Continuous measurements were compared using Bland and Altman analysis and Kappa statistics were used for comparison of categorical data.

The right ventricle to pulmonary artery interaction factor (RVPA) was created to evaluate if there was any prognostic impact of having a dilated RV, with a normal sized main pulmonary artery. The RVPA interaction factor was calculated thus; RV:LV ratio ÷ MPAD:Ao ratio. The theory being that a main pulmonary artery takes time to dilate, and implies RV to pulmonary artery coupling is maintanined. Pulmonary function trends from the previous year were also interogated to assess if there was any difference in lung function decline in relation to the RVPA interaction factor patients with available data.

6.3 Results

6.3.1 Patient demographics

179 patients were included within the study between 2005 and 2015; median interval between CTPA and RHC was 0.0[-0.2 to 0.0] months, with a mean age of 62±11 years; 53.5% were male (table 6.1). At RHC PH was present in n = 145 (81%). PH was mild – moderate in n = 69 (39%), and severe in n = 76 (42%). ILD diagnoses included: IPF (n=58), CTD-ILD (n=49), sarcoidosis (n=34), CHP (n=13), NSIP (n=13) and other interstitial lung diseases (n=12) (table 6.2).

	CTPA Cohort (n=179)
Age, years	62±11
Gender, n (%) men	97 (54)
ILD diagnosis n (%)	
IPF	58 (32)
CTD	49 (28)
Sarcoidosis	34 (19)
Other ILD	12 (7)
CHP	13 (7)
NSIP	13 (7)
Right heart catheter	
mPAP (mmHg)	33±10
PVR (Wood Units)	6.0±3.7
CO (L/min/m^2)	4.3 ±1.2
PCWP (mmHg)	10±5
BNP (ng/L)	99[43-266]
Pulmonary function tests	
FEV1 (% predicted)	57±18
FVC (% predicted)	60±20
TLco (% predicted)	24±10
Kco (% predicted)	51±17
Composite physiological index	63±11
Alveolar arterial gradient	6.0±2.2
CT scan	
ILD severity	43±14

Table 6.1. Baseline right heart catheter and non-invasive variables.

Abbreviations: mPAP - mean pulmonary pressure at right heart catheter, PVR - Pulmonary vasular resistance, BNP - Brain natriuretic peptide, FEV1 - Forced expiratory volume in one second, FVC - Forced vital capacity, TLCO - Transfer factor, KCO - Transfer coefficient, PaO_2 - Arterial Oxygen content obtained by capillary blood gas analysis. Data are mean±SD or median [inter-quartile range].

Connective Tissue Disease	Number	Other ILD	Number
Scleroderma	18	Unclassifiable ILD	3
Rheumatoid Arthritis	8	Smoking related ILD	3
Mixed connective tissue disease	4	Fibrotic organising pneumonia	1
Antisynthetase syndrome	6	Langerhans cell histiocytosis	1
UCTD	9	PPFE	1
Systemic lupus erythematous	2	Lymphangioleiomyomatosis	2
Sjogrens syndrome	2	Pulmonary alveolar proteinosis	1

Table 6.2. Classification of connective tissue disease and "Other" interstitial lung disease

Abbreviations: UCTD - Undifferentiated connective tissue disease.

6.3.2 CTPA measurements compared in pulmonary hypertension severity groups

Measurements performed at CTPA were compared between PH severity groups. The PH severity groups were defined as 1) no PH (<25mmHg), 2) mild – moderate PH (≥25-34mmHg) and 3) severe PH (≥35mmHg). MPAD showed a stepwise increase in mean values with increasing severity of PH. In addition, all groups were significantly different from each other (table 6.3). However, when the MPAD was combined with the aorta diameter, the MPAD:AA ratio was only significantly different between patients without PH and patients with severe PH (1.01[0.9-1.1 vs 1.10[1.0-1.2], p=0.002). Patients with severe PH had significantly larger RV*axial* measurements than patients without PH, and patients with mild to moderate PH (p<0.001 for no PH vs severe PH and p=0.006 for mild to moderate PH vs severe PH). Correspondingly, the RV:LV*axial* ratio was significantly larger in patients with severe PH compared to patients with no PH and patients with mild to moderate PH (p<0.001 for both), although no significant difference was present between patients without PH and mild to moderate PH (p=0.2). The RV*largest* measurements and RV:LV*largest* ratio demonstrated the same trends between PH groups. The LVlargest measurements were smaller in patients with severe PH vs mild to moderate PH (p<0.001). Both RA*longitudinal* diameter and RA*transeverse* diameter were larger in patients with severe PH compared to patients without PH and patients with mild to moderate PH. LA diameter was not significantly different between any PH severity group (p=0.1), although there was a trend toward smaller LA size in patients without PH. VSB occurred in n= 6 (38%) of patients without PH versus n=45 (76%) of patients with severe PH (P<0.001). The presence of IVC reflux was again different between patients without PH compared to patients with severe

PH ($p<0.001$) and between patients with mild to moderate PH compared to patients with severe PH ($p=0.001$); but not between patients without PH and patients with mild to moderate PH ($p=0.4$). Systolic RV:LV ratio at echo was larger when comparing patients without PH with patients with severe PH (0.83[0.6-0.9] vs 1.52[0.9-1.9], $p<0.001$), and patients with mild to moderate PH with patients with severe PH (0.86[0.6-0.9] vs 1.52[0.9-1.9], $p<0.001$).

	mPAP <25mmHg (n=34)	mPAP ≥25 - 34mmHg (n=69)	mPAP ≥35mmHg (n=76)	P value	No PH vs MM PH	No PH vs Severe PH	Severe PH vs MM PH
	No PH	**MM PH**	**Severe PH**				
Main PA diameter (mm)	31±5	34±4	36±4	<0.001	0.02	<0.001	0.007
Aorta Diameter (mm)	31±4	32±3	32±4	0.3	-	-	-
MPAD:AA ratio	1.01 [0.9-1.1]	1.06 [1.0-1.1]	1.10 [1.0-1.2]	0.001	0.2	0.002	0.08
RV*axial* diameter (mm)	39±8	42±9	47±9	<0.001	0.3	<0.001	0.006
LV*axial* diameter (mm)	37±8	36±7	33±7	0.03	0.8	0.07	0.09
RV:LV*axial* ratio	1.02 [0.9-1.3]	1.18 [1.0-1.4]	1.41 [1.1-1.7]	<0.001	0.2	<0.001	<0.001
RV*largest* diameter (mm)	46±9	49±8	54±9	<0.001	0.1	<0.001	0.003
LV*largest* diameter (mm)	39±7	41±7	37±7	0.002	0.8	0.09	<0.001
RV:LV*largest* ratio	1.09 [0.9-1.4]	1.25 [1.0-1.5]	1.47 [1.2-1.8]	<0.001	0.7	<0.001	<0.001
RA*longitudinal* diameter (mm)	44±8	47±11	51±10	<0.001	0.4	0.002	0.02
RA*transeverse* diameter (mm)	53±11	56±10	65±14	<0.001	0.7	<0.001	<0.001
LA diameter (mm)	34±9	38±9	37±7	0.1	-	-	-
RA:LA ratio	1.60 [1.3-1.9]	1.42 [1.2-1.7]	1.8 [1.4-2.3]	0.005	0.9	0.2	0.005
Ventricular septal bowing (VSB) (n/%)	6/18	17/25	46/61	<0.001	0.3	<0.001	0.001
IVC diameter (mm)	25±6	24±7	29±6	<0.001	0.9	0.001	<0.001
IVC reflux (n/%)	16/47	38/55	62/84	<0.001	0.4	<0.001	0.001
RV:LV*echo*	0.83 [0.6-0.9]	0.86 [0.6-0.9]	1.52 [0.9-1.9]	<0.001	0.9	<0.001	<0.001

Table 6.3. **CTPA measurements stratified by PH severity**

Abbreviations: mPAP - mean pulmonary artery pressure, PH - pulmonary hypertension, MM - mild-moderate, PA - pulmonary artery, MPAD - main pulmonary artery diameter, RV - right ventricle, LV - left ventricle, RA - right atrium, LA - Left atrium, IVC - Inferior vena cava. Groups compared with analysis of variance, Kruskal-Wallis or Chi squared test as appropriate. Where a significant difference was found between the groups, post hoc testing was performed with Tukey honest significant difference, or paired Wilcoxon with adjustment of the p-value to account for multiple testing.

6.3.3 Correlation of measurements performed at CTPA with other variables

The RV:LV ratio measured at CTPA correlated modestly with mPAP and PVR (Table 6.4). Modest correlation was also demonstrated with all echocardiographic measures of pulmonary pressure and function. Strong correlation was seen with the RV:LV ratio measured at echo and eccentricity index. No significant correlation was seen with spirometric measures of lung function and a weak correlation was seen with both TLco and Kco.

	RV:LV*axial* ratio		RV:LV*largest* ratio	
	Spearman's Correlation	**P value**	**Spearman's Correlation**	**P value**
Right heart haemodynamic measurements				
mPAP (mmHg)	0.43	<0.001	0.42	<0.001
PVR (Wood units)	0.46	<0.001	0.49	<0.001
Cardiac Output (L/m)	-0.14	0.06	-0.20	0.01
Echocardiographic measurements				
RVSP (mmHg)	0.37	<0.001	0.36	<0.001
Right atrial Area (cm^2)	0.41	<0.001	0.41	<0.001
RV:LV short axis ratio (systolic)	0.61	<0.001	0.59	<0.001
Fractional area change (%)	-0.39	<0.001	-0.35	<0.001
TAPSE (m/s)	-0.33	<0.001	-0.34	<0.001
Eccentricity Index	0.55	<0.001	0.50	<0.001
Pulmonary function Tests				
FEV_1 (% predicted)	0.05	0.6	0.04	0.6
FVC (% predicted)	0.00	0.9	0.01	0.9
TLco (% predicted)	-0.19	0.02	-0.22	0.006
Kco (% predicted)	-0.23	0.004	-0.29	<0.001
Composite physiological index	0.14	0.09	0.14	0.08
Alveolar arterial gradient	0.37	<0.001	0.36	<0.001
Brain natriuretic peptide				
BNP (ng/L)	0.34	<0.001	0.38	<0.001

Table 6.4. Correlation of CTPA measurements with other invasive and non-invasive variables.

Abbreviations: mPAP - mean pulmonary pressure, PVR - Pulmonary vascular resistance, RVSP - Right ventricular systolic pressure, RV - right ventricle, LV - Left ventricle, TAPSE - Trans-annular systolic plane excursion, FEV_1 - Forced expiratory volume in one second, FVC - Forced vital capacity, TLco - Transfer factor, Kco - Transfer coefficient. Correlation performed with Spearman correlation, strength of correlation graded as follows: >0.5, large, 0.5 – 0.3, moderate 0.3 – 0.1 small and <0.1 trivial.

6.3.4 Inter-observer variability of the CTPA measurements

The CTPA measurements and ancillary signs were compared in 60 patients (table 6.5). The mean difference between analysers for the RV*largest* was 1.8mm (-10 to 14.3mm) (figure 6.1 / Table 6.5). The largest LV diameter mean difference between analysers was -1.3mm (-4.5 to 5.0mm). The RV:LV*largest* ratio mean difference between analysers was 0.02 (-0.4 to 0.4). Other measurement comparisons are shown in table 6.5. Kappa statistics demonstrated that there was fair agreement for the presence of a bowed septum (Kappa (K):0.26, p=0.003). Agreement was substantial, with subjective evaluation of the RV being larger than the LV (K:0.77, p<0.001) and when the RV:LV*largest* ratio was regarded as a binary categorical variable with an RV:LV ratio of ≥1.0 (K:0.65, p<0.001).

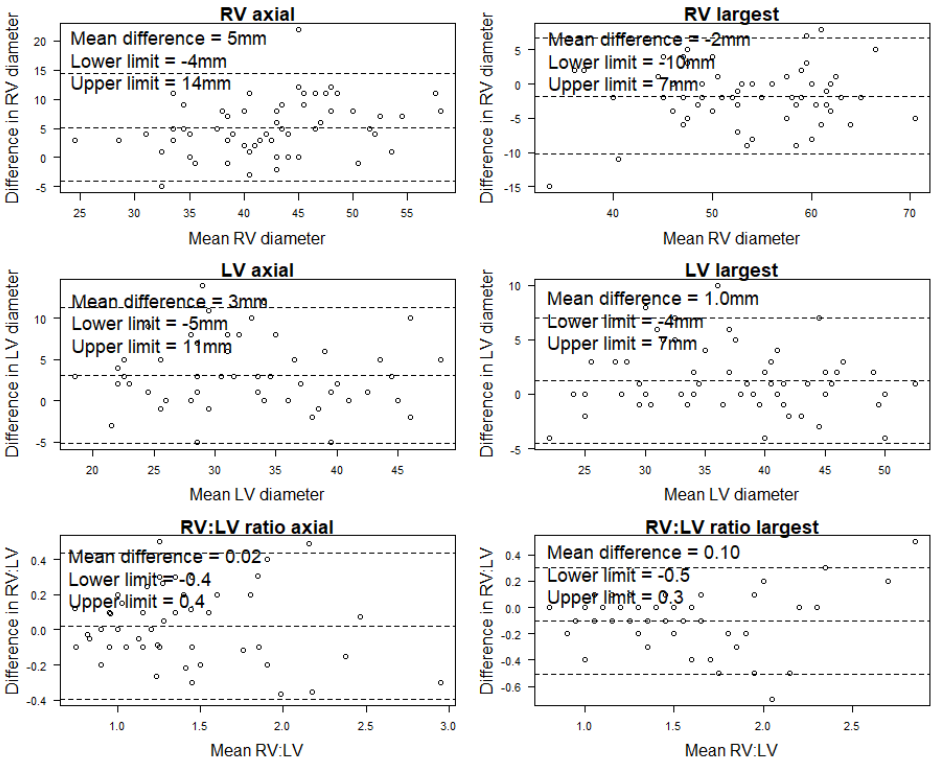


Figure 6.1. Bland-Altman comparison of inter-observer measurements for axial and largest measurements.

Abbreviations: RV - Right ventricle, LV - Left ventricle.

	Bland-Altman analysis	
	Mean difference (mm)	**95% CI (mm)**
RV*axial* diameter	5.2	-4 to 14
LV*axial* diameter	3.1	-5 to 11
RV:LV*axial* ratio	0.1	-0.5 to 0.3
RV*largest* diameter	1.8	-10 to 6.7
LV*largest* diameter	1.3	-4.5 to 7.0
RV:LV*largest* ratio	0.02	-0.4 to 0.4
RA*longitudinal* diameter	1.0	-10 to 13
RA*transeverse* diameter	1.2	-16 to 19
	Kappa comparison of RV:LV thresholds	
	Kappa	p-value
Subjective RV	0.77	<0.001
RV:LV*axial* ratio ≥ 1.0	0.52	<0.001
RV:LV*largest* ratio ≥ 1.0	0.65	<0.001
Bowed Septum	0.26	0.003

Table 6.5. Bland-Altman comparison of inter-observer measurements for axial and largest measurements, and Kappa values for comparison of categorical variables

Abbreviations: RV - Right ventricle, LV - Left ventricle.

6.3.5 The ability of CTPA derived measurements to predict PH in suspected ILD-PH

Pulmonary hypertension (≥25mmHg) was present in n=145, (81%) of the cohort. The RV:LV ratio had good sensitivity for predicting PH: RV:LV*axial* ≥1.0 had a sensitivity of 81%; RV:LV*largest* ≥1.0 had a sensitivity of 86% (Table 6.6). However, as RV dilatation also occurred in patients without PH, the RV:LV ratio lacked specificity: RV:LV*axial* ≥1.0 had a specificity of 46 %; RV:LV*largest* ≥1.0 had a specificity of 32%. RA measurements performed poorly in predicting PH. The presence of a bowed septum had a low sensitivity for predicting PH (43%), although a high specificity (84%).

	PH at RHC		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Odds ratio (95% CI)	p-value				
Main PA diameter (mm)	1.21 (1.12-1.32)	<0.001†	-	-	-	-
MPAD ≥ 32 mm	4.58 (2.42-8.85)	<0.001	74	60	88	37
MPAD:Ao	1.51 (1.19-1.94)	0.005†	-	-	-	-
MPAD:Ao ratio ≥ 1.0	2.56 (1.07-3.80)	0.06	-	-	-	-
RV:LV*axial* ratio	1.20 (1.09-1.33)	0.003†	-	-	-	-
RV:LV*axial* ratio ≥ 1.0	3.91 (2.04-7.53)	0.0006	81	46	85	39
RV:LV*largest* ratio	1.21 (1.10-1.35)	0.002†	-	-	-	-
RV:LV*largest* ≥ 1.0	3.12 (1.52-6.29)	0.008	86	32	83	38
RV subjectively larger than LV	4.03 (2.12-7.75)	<0.001†	77	53	87	37
RA*longitudinal* diameter (mm)	1.05 (1.01-1.08)	0.02†	-	-	-	-
RA*longitudinal* ≥ 50 mm	2.28 (1.20-4.48)	0.04	50	70	87	27
RA*transeverse* diameter (mm)	1.04 (1.01-1.07)	0.01†	-	-	-	-
RA*transeverse* ≥ 50mm	1.82 (0.91-3.53)	0.1	-	-	-	-
VSB	4.76 (2.17-11.9)	0.002†	43	84	91	27
IVC reflux	2.61 (1.38-4.99)	0.01†	70	54	86	31

Table 6.6. Logistic regression and sensitivity and specificity analysis for CTPA values ability to predict PH at RHC.

Abbreviations: PPV - Positive predictive value, NPV - Negative predictive value, MPAD - Main pulmonary artery diameter, Ao - Aorta, RV - right ventricle, LV - Left ventricle, RA - Right atrium, VSB - ventricular septal bowing, IVC - Inferior vena cava reflux of contrast. †Remained independent predictors of PH at RHC after adjusting for: FVC, ILD diagnosis, age, and gender.

6.3.6 The ability of CTPA derived measurements to predict severe pulmonary hypertension in suspected ILD-PH

Severe PH (≥35mmHg) was present in n=76, (42%) of the cohort. The RV:LV*axial* ≥1.0, and RV:LV*largest* ≥1.0 measurements had high sensitivities however low specificities (table 6.7). By combing the variables, it was possible to improve the specificity while retain an acceptable sensitivity in detecting severe PH. If patients had both an RV:LV*largest* ≥ 1.2 and IVC reflux of contrast, the odds ratio of severe PH was 6.43 (CI:3.75 to 11.3), and predicted severe PH with an sensitivity of 71%, specificity of 72%, a PPV of 65% and a NPV of 78%.

	Severe PH at RHC		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Odds ratio (95% CI)	p-value				
Main PA diameter (mm)	1.18 (1.10-1.26)	<0.001†	-	-	-	-
MPAD ≥ 32 mm	3.78 (2.11-7.01)	0.001	83	44	52	78
MPAD:AA	1.51 (1.27-1.84)	<0.001†	-	-	-	-
MPAD:AA ≥ 1.0	1.52 (0.89-2.65)	0.2	-	-	-	-
RV:LV*axial* ratio	1.19 (1.11-127)	<0.001†	-	-	-	-
RV:LV*axial* ratio ≥ 1.0	3.72 (1.94-7.59)	0.001	88	33	49	80
RV:LV*largest* ratio	1.26 (1.17-1.37)	<0.001†	-	-	-	-
RV:LV*largest* ≥ 1.0	3.08 (1.50-6.87)	0.01	86	38	50	78
RV:LV*largest* ≥ 1.2	3.56 (2.03-6.42)	<0.001	80	47	52	77
RV:LV*largest* ≥ 1.5	3.38 (1.97-5.86)	<0.001	49	78	62	68
RV subjectively larger than LV	4.47 (2.40-8.82)	<0.001†	87	40	52	81
RA*longitudinal* diameter (mm)	1.06 (1.03-1.09)	<0.001†	-	-	-	-
RA*longitudinal* ≥ 50 mm	2.78 (1.67-4.66)	0.001	61	64	55	69
RA*transeverse* diameter (mm)	1.07 (1.04-1.9)	<0.001	-	-	-	-
RA*transeverse* ≥ 50mm	2.63 (1.41-5.10)	0.01	86	31	47	74
VSB	5.18 (3.02-9.02)	<0.001†	59	78	66	73
IVC reflux	4.69 (2.59-8.86)	<0.001†	84	49	55	80
RV:LV*largest* ≥ 1.2 and IVC reflux of contrast	6.43 (3.75-11.3)	<0.001	71	72	65	78

Table 6.7. Logistic regression and sensitivity and specificity analysis for CTPA values ability to predict mild to moderate PH at RHC

Abbreviations as per table 6.6. †Remained independent predictors of PH at RHC after adjusting for: FVC, ILD diagnosis, age, and gender.

6.3.7 Prognostication with demographics, haemodynamics, pulmonary function tests and echocardiography

133 (74%) patients died or underwent lung transplantation within 5 years of undergoing RHC. 11 (6%) patients underwent lung transplantation and 122 (68%) patients died. Median follow up was 2.23[0.9-4.2] years. Age at RHC predicted outcome (HR:1.28, CI: 1.09-1.51, p=0.003), per ten-year increase in age (table 6.8). A diagnosis of IPF was a strong adverse prognostic factor (HR:2.82, CI:1.97-4.03, p<0.001). Neither mPAP nor PVR (as a continuous variable) were associated with an adverse outcome, A diagnosis of PH was not associated with an adverse outcome, although the very high prevalence of PH confounds this analysis.

The following pulmonary function tests predicted mortality: FVC (HR: 0.93, CI:0.98-0.99, p=0.004), TLco (HR: 0.93, CI:0.91-0.95, p<0.001) and Kco (HR: 0.98, CI:0.97-0.99, p=0.001), for each increase 1% in percent predicted value. The CPI predicted mortality (HR: 1.07, CI:1.05-1.09, p<0.001) for each one-point increase.

168 patients had an echocardiogram within 6 months of their CTPA; interval 1.4±1.7 months. RV:LV ratio could be measured in 134 (74%). The following echocardiographic variables predicted mortality TAPSE <1.6m/s (HR: 0.97, CI:1.06-2.24, p=0.02), and a systolic RV:LV (short-axis view) ≥1.0 (HR: 1.57, CI:1.52-2.32, p=0.03). However, RVSP, RA area, FAC and eccentricity index did not predict mortality.

Demographics	Hazard ratio (95% CI)	p-value
Age (per 10-year increase)	1.28 (1.09-1.51)	0.003
Male gender	1.72 (1.21-2.43)	0.002
Idiopathic pulmonary fibrosis diagnosis	2.82 (1.97-4.03)	<0.001
Right heart catheter haemodynamics		
Mean pulmonary artery pressure (mmHg)	1.00 (0.98-1.01)	0.6
Pulmonary Hypertension (≥25mmHg)	1.15 (0.74-1.79)	0.2
Pulmonary vascular resistance (Wood units)	1.02 (0.98-1.07)	0.4
Cardiac Output (L min)	0.88 (0.75-1.02)	0.09
Pulmonary function tests – performed in 168 of the cohort		
FEV_1 (% predicted)	0.99 (0.99-1.00)	0.9
FVC (% predicted)	0.99 (0.98-0.99)	0.004
TLco (% predicted)	0.93 (0.91-0.95)	<0.001
Kco (% predicted)	0.98(0.97-0.99)	0.001
Composite physiological index	1.07 (1.05-1.09)	<0.001
Echocardiographic Variables – performed in 175 of the cohort		
Right ventricular systolic pressure (mmHg)	1.00 (0.99-1.01)	0.5
Right atrial area (cm^2)	1.01 (0.98-1.03)	0.5
Trans annular systolic plane excursion (TAPSE) (cm)	0.97 (0.93-1.01)	0.09
TAPSE <1.6 (cm)	1.54 (1.06-2.24)	0.02
RV Fractional area change (%)	1.01 (0.99-1.04)	0.3
Eccentricity Index	1.22 (0.83-1.79)	0.3
RV:LV*echo* ratio (short axis view, systolic) (per 0.1 increase)	1.02(0.99-1.01)	0.1
RV:LV*echo ratio* ≥ 1.0	1.57 (1.52-2.32)	0.03

Table 6.8. Cox proportional hazard regression to assess the effect of demographics, haemodynamics, PFT and echocardiography on mortality in patients suspected of having ILD-PH.

Abbreviations: FEV_1 - Forced expiratory volume in one second, FVC - Forced vital capacity, TLco - gas-transfer, Kco - Gas transfer co-efficient, RV - Right ventricle, LV - Left ventricle. Cox regression analysis was used with the date as start of the follow up as the date of the investigation being tested and followed up over 5 years or censorship occurred at last clinical contact. RV:LV*echo* ratio was available in 125 of the 175 echocardiograms performed.

6.3.8 Prognostic implications of CTPA variables and severity of fibrosis

Severity of fibrosis predicted mortality (HR:1.33, CI: 1.17-1.51, p<0.001), per 10% increase in ILD extent at CT (table 6.9). MPAD expressed as a continuous variable did not predict mortality. There was a trend toward an increased MPAD:Ao ratio being associated with a better prognosis (HR:0.90, CI: 0.81-1.01, p=0.07). As per analysis in Chapter 3 (section 3.4.1)

patients with severe PH were more likely to have an increased MPAD:Ao ratio compared to both patients without PH (p=0.005), and patients with mild-moderate PH (p<0.001). These patients were more likely to have a favourable ILD diagnosis (Sarcoid/CTD-ILD) and more likely to be treated with vasodilators. The RV*axial* diameter did not predict mortality, however when combined with LV into the RV:LV*axial* ratio predicted mortality (HR:1.06, CI:1.02-1.10, p< 0.001) per 0.1 increase in the RV:LV ratio (for example by increasing from 0.8 to 0.9). An RV:LV*axial* ratio ≥1.0 predicted mortality (HR:2.06, CI:1.32-3.21, p=0.001) (figure 6.2, panel A). With regard to the RV*largest* measurements the following predicted mortality: (HR:1.02, CI:1.00-1.04, p=0.02) per 0.1mm increase in RV diameter, the RV:LV*largest* ratio predicted mortality (HR:1.06, CI:1.02-1.10, p = 0.003) per 0.1 increase in the RV:LV ratio, an RV:LV*largest* ratio ≥1.0 predicted mortality (HR:2.43, CI:1.39-4.24, p = 0.002)(figure 6.2 panel B). Both RA*longitudinal* and RA*transverse* diameter predicted mortality as a continuous measurement, although a threshold which reliably predicted mortality could not be found. The presence of VSB was an adverse sign (HR:1.41, CI:1.00-2.00, p = 0.05), (figure 6.2 panel C). Reflux of contrast into the IVC did not predict mortality. The presence of either an RV:LV*largest* ratio ≥1.0 or an RA longitudinal size ≥50mm was associated with mortality (HR:3.08, CI:1.56-6.07, p = 0.001) (figure 6.2 panel D).

CT Variables	PH at RHC	
	Hazard ratio (95% CI)	p-value
Severity of fibrosis (per 10% increase in extent)	1.33 (1.17-1.51)	<0.001
Main pulmonary artery diameter (MPAD) (mm)	1.00 (0.97-1.04)	0.8
MPAD:Aorta ratio	0.90 (0.81-1.01)	0.07
RV*axial* diameter (mm)	1.02 (0.99-1.04)	0.1
RV:LV*axial* ratio (per 0.1 increase)	1.06 (1.02-1.10)	<0.001
RV:LV*axial* ratio ≥ 1.0	2.06 (1.32-3.21)	0.001
RV*largest* diameter (mm)	1.02 (1.00-1.04)	0.02
RV:LV*largest* ratio (per 0.1 increase)	1.06 (1.02-1.10)	0.003
RV:LV*largest* ratio ≥ 1.0	2.30 (1.36-3.88)	0.002
RV subjectively larger than LV	1.91 (1.25-2.90)	0.003
RA*longitudinal* diameter (per mm increase)	1.02 (1.01-1.04)	0.01
RA*longitudinal* diameter ≥ 50mm	1.36 (0.97-1.92)	0.08
RA*transeverse* diameter (mm)	1.01 (1.00-1.03)	0.05
Ventricular septal bowing	1.41 (1.00-2.00)	0.05
Inferior vena cava reflux of contrast	1.32 (0.90-1.91)	0.2
RV:LV*largest* ≥ 1.0 or RA*longitudinal* ≥ 50 mm	3.08 (1.56-6.07)	0.001

Table 6.9. Cox proportional hazard regression to assess the effect of CT derived variables on mortality in patients suspected of having ILD-PH.

Abbreviations: RV - Right ventricle LV - Left ventricle, RA - Right atrium. Cox regression analysis was used with the date as start of the follow up as the date of the CTPA and followed up over 5 years or censorship occurred at last clinical contact.

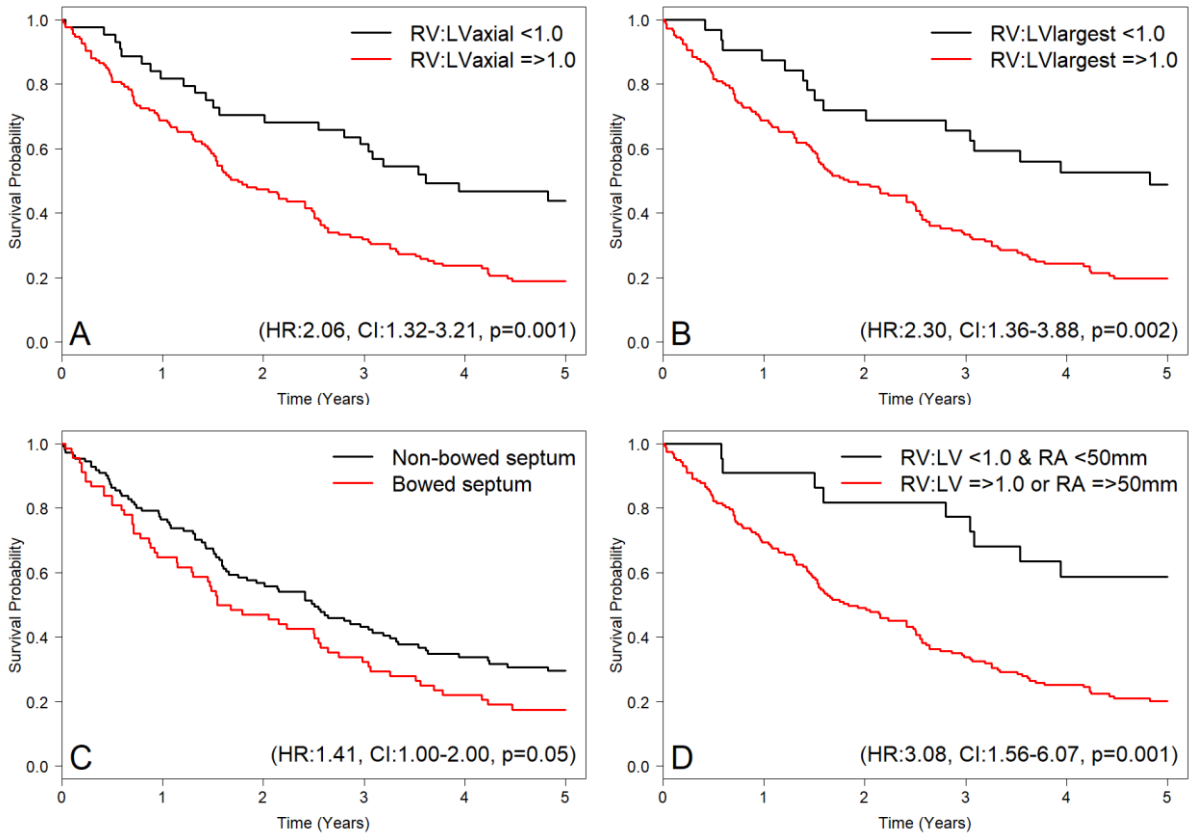


Figure 6.2. Kaplan Meier plots demonstrating estimated outcome plots for the RV:LV ratio

Abbreviations: RV - Right ventricle LV - Left ventricle, RA - Right atrium, HR - Hazard ratio, CI - Confidence interval. Panel A. RV:LV*axial* ratio ≥1.0, panel B. RV:LV*largest* ratio ≥1.0, panel C. Ventricular septal bowing, panel D. RV:LV*largest* ratio ≥1.0 or an RA longitudinal size ≥50mm. Cox regression analysis was used with the date as start of the follow up as the date of the CTPA and followed up over 5 years or censorship occurred at last clinical contact, survival has been estimated and plotted using Kaplan Meier plots.

6.3.9 Multivariable assessment of mortality

The multivariable model included age, severity of fibrosis at CT, IPF diagnosis and the RV:LV*largest* ratio (as a continuous variable). The RV:LV*largest* (table 6.10) ratio remained an independent predictor of mortality both as a continuous measurement (HR:1.04, CI:1.01-1.08, p = 0.03, per 0.1 increase), and as a threshold RV:LV*largest* ratio ≥1.0 (HR:1.83, CI:1.08-3.13, p = 0.03).

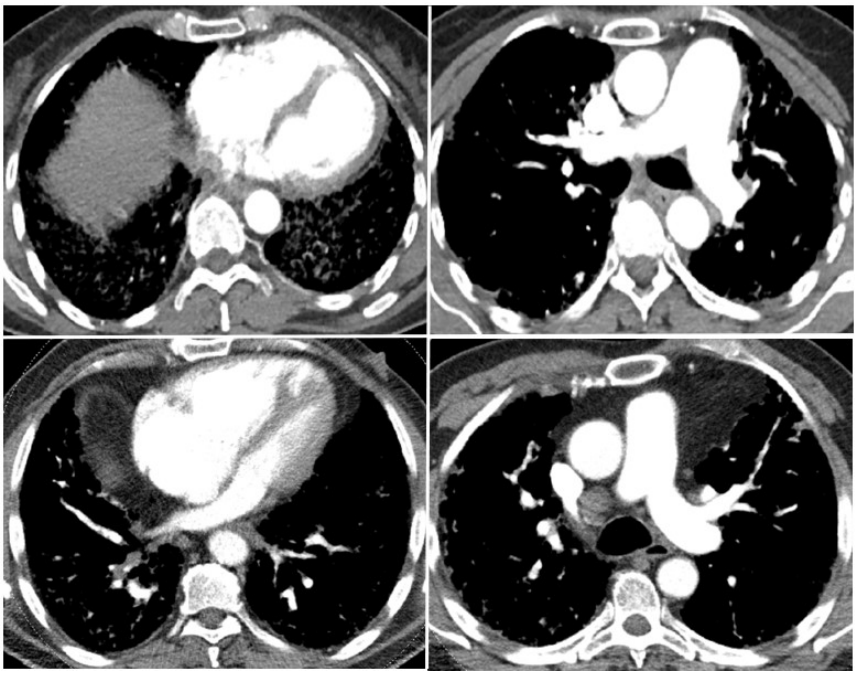
	Hazard ratio	Confidence interval	P value
Multivariable model - RV:LV*largest* ratio as a continuous variable			
Age at right heart catheter (per 10y increase)	1.27	1.06-1.53	0.01
Lobar fibrosis score (per 10% increase)	1.31	1.14-1.50	<0.001
IPF diagnosis	2.17	1.48-3.20	<0.001
RV:LV*largest* ratio	1.04	1.01-1.08	0.03
Multivariable model - RV:LV*largest* ratio ≥1.0			
Age at right heart catheter (per 10y increase)	1.26	1.05-1.51	0.01
Lobar fibrosis score (per 10% increase)	1.29	1.13-1.48	<0.001
IPF diagnosis	2.21	1.49-3.25	<0.001
RV:LV*largest* ratio ≥1.0	1.83	1.08-3.13	0.03

Table 6.10. Multivariable adjustment for the RV:LV*largest* ratio, as both a continuous measurement and as a RV:LV*largest* ratio ≥1.0 threshold

Abbreviations: IPF - Idiopathic pulmonary fibrosis, RV - Right ventricle, LV - Left ventricle. Multivariable model using cox-regression analysis (CTPA date as start of follow up). The first multivariable model (consisting of age, ILD diagnosis of IPF, lobar fibrosis severity and the RV:LV ratio). The RV:LVlargest ratio ≥1.0 also remained an independent predictor after adjustment in the multivariable model.

6.3.10 Right ventricle to pulmonary artery interaction factor

The right ventricle to pulmonary artery (RVPA) interaction factor was created to evaluate the interaction between the main pulmonary artery and the RV. The RVPA interaction factor was calculated as per figure 6.3. A RVPA interaction factor <1.0 would result from a preserved RV diameter and an enlarged MPAD (assuming the corresponding LV and aorta diameter was not enlarged). A RVPA interaction ≥1.0 factor would result from an enlarged RV, without a corresponding enlarged MPAD.



Calculation of the RV PA interaction factor
RV:LV*largest* = 0.97
MPAD:Ao = 1.28
0.97 ÷ 1.28 = 0.76
RV PA interaction factor = 0.7

Calculation of the RV PA interaction factor
RV:LV*largest* = 2.0
MPAD:Ao = 0.96
2.00 ÷ 0.96 = 2.09
RV PA interaction factor = 2.09

Figure 6.3. Calculation of the RVPA interaction factor.

Abbreviations: RV - Right ventricle LV - Left ventricle, MPAD - Main pulmonary artery diameter, AO - Aorta, PA - Pulmonary artery.

An RVPA interaction factor ≥1.0 was associated with mortality (HR:2.06, CI:1.30-3.25, p=0.002) (figure 6.4). The RVPA interaction factor remained an independent predictor after being adjusted for age, ILD diagnosis and fibrosis score at CT (HR:1.95, CI:1.20-3.16,

p=0.006). Patients with an RVPA interaction factor ≥1.0 were more likely to be male (p=0.03) (table 6.11). In terms of haemodynamics mPAP was higher (p=0.05), PVR was higher (p<0.001) although the number of patients classified as having PH (≥25mmHg) was not different (p=0.5). Spirometric tests were not different between the groups however TLco (p=0.02), Kco (p=0.003) were lower and the CPI (p=0.003), and Aa gradient were higher (p<0.0001) in patients with an RVPA interaction factor ≥1.0. ILD severity was not worse in patients with a RVPA interaction factor ≥1.0 (p=0.1). The aorta diameter was larger (p<0.001), and MPAD:Ao ratio was smaller (p=0.04), the RV*largest* diameter (p<0.001), and RV*largest* ratio (p<0.001) were larger. There was no difference in the ILD diagnostic groups (p=0.08). Longitudinal pulmonary function trends were available in 69 patients, 23 with an RVPA interaction factor <1.0, and 46 with an RVPA interaction factor >1.0. Relative decline in FVC was larger in patients whose RVPA interaction factor was ≥1.0; -11±11% versus -5±10% (p=0.03). Decline in gas transfer was also higher in patients whose RVPA interaction factor was ≥1.0; -22±18% versus -11±17% (p=0.02).

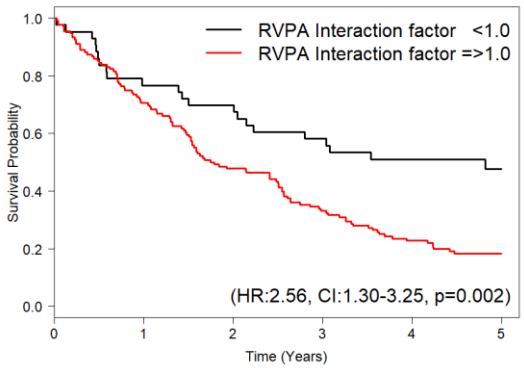


Figure 6.4. Kaplan-Meier plots – Prognostic significance of the right ventricle to pulmonary artery interaction factor.

Abbreviations: RVPA - Right ventricle to pulmonary artery interaction factor, HR - Hazard ratio, CI - confidence interval.

	RV PA interaction factor <1.0	RV PA interaction factor ≥1.0	p-value
Number	43	136	
Age, years	59±12	63±11	0.1
Gender, n (%) men	17 (40)	80 (59)	0.03
ILD diagnosis n (%)			
Idiopathic pulmonary fibrosis	9 (21)	46 (34)	
Connective tissue disease	18 (42)	31 (23)	
Sarcoidosis	6 (14)	28 (20)	0.08
Other ILD	5 (12)	10 (7)	
Chronic hypersensitivity pneumonitis	4 (9)	9 (7)	
Non-specific interstitial pneumonitis	1 (2)	12 (9)	
Right heart catheter			
Mean pulmonary artery pressure (mmHg)	31±8	34±8	0.05
Pulmonary hypertension (25mmHg)	33 (77)	112 (82)	0.5
Pulmonary vascular resistance (Wood Units)	4.4±2.1	6.5±3.9	0.001
Cardiac output (L/min/m^2)	4.6±1.3	4.2±1.2	0.2
Pulmonary capillary wedge pressure (mmHg)	10±4	9±5	0.1
Brain natriuretic peptide (ng/L)	72[38-114]	120[44-404]	0.02
Pulmonary function tests			
FEV1 (% predicted)	55±19	58±17	0.4
FVC (% predicted)	60±22	60±19	0.9
TLco (% predicted)	28±12	23±8	0.02
Kco (% predicted)	58±17	49±16	0.003
Composite physiological index	59±14	64±10	0.003
Alveolar arterial gradient	4.8±2	6.4±2	<0.001
Preceding pulmonary function tests ≠			
Relative decline in FVC (% predicted)	-5±10	-11±11	0.03
Relative decline of 10% in FVC (n/total (%))	8/23 (35%)	26/46 (57%)	0.1
Relative decline in TLco (% predicted)	-11±17	-22±18	0.02
Relative decline of 10% in TLco (n/total (%))	10/23 (43)	32/44 (73)	0.04
CT scan			
ILD severity	40±15	44±14	0.1
Main pulmonary artery diamter (MPAD) (mm)	33±5	34±5	0.3
Aorta diameter (mm)	30±3	33±4	<0.001
MPAD:Aorta diamter	1.10[1.0-1.2]	1.07[0.9-1.2]	0.04
RV*largest* diameter (mm)	41±7	54±8	<0.001
RV:LV*largest ratio*	0.93[0.82-1.05]	1.46[1.24-1.66]	<0.001

Table 6.11. Patient stratified by an RVPA interaction factor ≥1.0

Abbreviations: RVPA - Right ventricle to pulmonary artery interaction factor, ILD - Interstitial lung disease, FEV_1 - Forced expiratory volume in one second, FVC - Forced vital capacity, TLco - gas-transfer, Kco - Gas transfer co-efficient, RV - Right ventricle, LV - Left ventricle. ≠Avaliable in 69 patients

6.3.11 Impact of the RV:LV ratio in different ILD diagnostic groups

The prognostic impact of the RV:LV*largest* ratio ≥1.0 was tested within ILD diagnostic groups. Patients with sarcoid were grouped with CTD-ILD patients (n=82) (because of similarities in clinical outcome), and patients with: IPF, NSIP, CHP, and "other" ILDs were grouped together (n=97). Treatment with vasodilators occurred in (n=60), 73% of the CTD-ILD/Sarcoid group versus (n=43), 44% of the non-CTD-ILD/Sarcoid group. The RV:LV*largest* ratio ≥1.0 predicted mortality in the non-CTD-ILD/sarcoid group (HR: 3.33, CI:1.59-6.96, p = 0.001) (figure 6.5, panel A), although did not predict mortality in the CTD-ILD/sarcoid group (HR: 1.51, CI:0.71-3.23, p = 0.3) (figure 6.5, panel B). However, a RV:LV*largest* ratio ≥1.2 did predict mortality in patients in the CTD/ILD group (HR: 2.07, CI:1.11-3.86, p = 0.03) (figure 6.5, panel C). Therefore, a hybrid predictor was created consisting of an RV:LV*largest* ratio ≥1.0 in patients with non-CTD/Sarcoid related ILD, and RV:LV*largest* ratio ≥1.2 (HybridRV:LV*largest*) in patients with CTD-ILD/Sarcoid. The HybridRV:LV*largest* ratio predicted mortality in the whole cohort (HR: 2.95, CI:1.86-4.67, p<0.001) (figure 6.5, panel D).

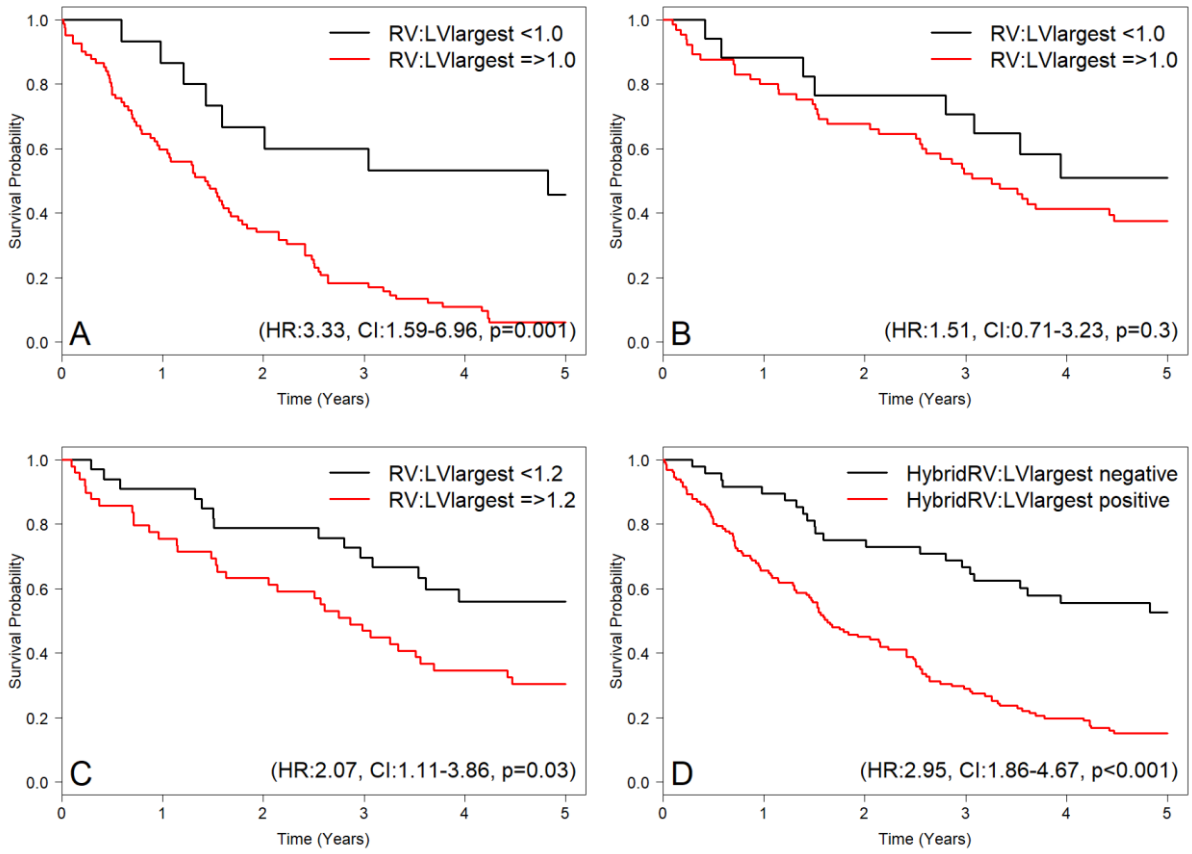


Figure 6.5. Kaplan-Meier plots demonstrating the RV:LV largest ratio in IIP and non-IIP ILD-PH

Panel A. RV:LV*largest* ratio ≥1.0 in IIP and CHP patients, panel B. RV:LV*largest* ratio ≥1.0 in CTD-ILD/sarcoid patients, panel C. RV:LV*largest* ratio ≥1.2 in CTD-ILD/sarcoid patients, panel D. HybridRV:L *largest* ratio (≥1.0 in IIP and CHP, and ≥1.2 in CTD-ILD/Sarcoid patients).

6.4 Conclusion

This is the first study which evaluates measurements performed at CTPA in their ability to both predict the presence of PH and prognosticate in patients with suspected ILD-PH. An enlarged RV:LV ratio at CTPA has a high sensitivity in predicting the presence of PH at RHC in patients with suspected ILD-PH (although the high prevalence of PH in the study group is a distinct limitation). The presence of an RV which is visually enlarged compared to the LV

provides a rapid assessment and useful information that PH is both likely and has prognostic implications. Formal measurement of the RV:LV ratio improves the prognostication with the finding that an RV:LV*largest* ratio ≥1.0 is strongly predictive of mortality (HR: 2.30, CI:1.36-3.88, p=0.002), and remains an independent predictor of mortality after adjusting for age, a diagnosis of IPF, and ILD severity. Many factors influence LV diameter, therefore the RV:LV ratio may be reduced despite significant PH due to co-existent diastolic cardiac dysfunction or ischaemic heart disease which are both more common in patients with IPF (Papadopoulos et al., 2008, Nathan et al., 2010). I sought to overcome this through the addition of gross RA dilatation (defined as a longitudinal RA diameter of ≥50mm) to an RV:LV ≥1.0, which both improved sensitivity in predicting PH and prognostication (HR:3.08, CI:1.56-6.07, p=0.001).

The RV:LV ratio measured at CTPA predicted outcome in patients within both CTD/sarcoid, and IIP/CHP patient groups ("Other" ILDs also within this group). Although, with different RV:LV thresholds, with IIP/CHP patients having a worse outcome with an RV:LV*largest* ratio ≥1.0 and patients with CTD/sarcoid a worse outcome with an RV:LV*largest* ratio ≥1.2. This finding could be explained by the fact that the use of vasodilators occurred in nearly three quarters of the CTD/sarcoid group versus less than half of IIP/CHP group. However, the significantly worse prognosis associated with the IIP/CHP diagnoses (especially IPF) will also affect the findings significantly. However, the higher RV:LV ratio predicting mortality in the CTD/sarcoid group supports the idea that these patients derive benefit from vasodilator therapy. I suspect that patients with CTD/sarcoid have a higher RV:LV ratio to predict outcome because they respond to vasodilator therapy and patients with RV:LV ratios ≥1.2

already have more severe RV impairment prior to initiation of treatment and therefore have worse outcome. If treatment of PH had little or no effect in these patients, then it is likely that outcome would be much more like the IIP/CHP groups, (especially as from my review in section 2.4 there were only small differences between the groups in term of lung function and ILD severity). Therefore, I would continue to suggest that any patient with a CTD/sarcoid and an RV:LV*largest* ratio ≥1.0 be investigated for PH (as it is highly likely that significant PH is present), rather than using the RV:LV*largest* ratio ≥1.2 threshold to provoke investigation. Prognosis in PAH is strongly linked to early diagnosis and optimal management with vasodilators (Galie et al., 2016). Therefore, these patients should be identified as early as possible and be treated as per current PAH guidelines.

The first study which evaluated intracardiac measures ability to predict PH was performed by Chan et al (Chan et al., 2011) although the study was carried out in 101 patients who were acutely ill requiring in-patient care (some of which were intubated), and 69% of the cohort had a primary cardiac diagnosis; therefore, comparison to this cohort does not seem appropriate. A study by Spruijt et al (Spruijt et al., 2015) recently evaluated 51 patients with pre-capillary PH and 25 non-PH patients as controls. Analysis was performed on both standard axial images (RV:LV*Spruijt*) (as occurred in our study with very similar methodology for RV measurement) and where images were reconstructed to a 4-chamber view (RV:LVrecon). RV:LV measurements in patients with PH were very similar regardless of the choice of method RV:LV*Spruijt* (1.62±0.42) and RV:LVrecon (1.65±0.42). The OR for predicting PH of the RV:LV*Spruijt* >1.2 measurement was (OR:2.26, CI:1.51-3.39,p=<0.001), and our RV:LV*largest* was similar (OR:3.86,CI:1.80-8.25,p=0.003). Their cut-off for predicting

pre-capillary PH using the RV:LV*Spruijt* ratio was 1.2, and when combined with MPAD:Ao ratio the area under the curve for predicting PH was 98%. Our cohort's demographics are different and the severity of PH in Spruijt et al cohort was more severe than ours as mPAP in their PH group was (48±16mmHg), compared to our PH group (37±9mmHg), which may account for the larger RV:LV ratio. The findings between the two studies that RV:LV ratio measured on standard CTPA are consistent and suggest that RV:LV measured at CTPA is a useful adjunct in PH risk stratification. Our analysis evaluating patients without PH, mild to moderate PH and severe PH (Section 6.3.2) shows that using CTPA measurements would be difficult to identify patients with PH. The occurrence of RV and RA dilatation was very similar in patients with mild-moderate and without PH. However, this study has shown that when the RV:LV ratio is increased outcome is worse (even when PH is not present) and therefore where RV dilatation is noted on CTPA potentially treatable condition such as PH and other contributing factors should be considered.

RV:LV ratio measured at CTPA is an accepted method of demonstrating RV dysfunction in acute PE (Konstantinides et al., 2014); a prospective trial in 457 patients, where RV dysfunction was defined as an RV:LV ratio of ≥0.9 (measured at valvular plane at different levels) predicted in-hospital death or clinical deterioration of (HR:3.5,CI:1.6-7.7, p=0.002)(Becattini et al., 2011). Our finding that the RV:LV*largest* ≥1.0 predicts mortality or lung transplant over 60 months of follow up (HR:2.30, CI:1.36-3.88, p = 0.002) mirrors these findings.

Inter-observer analysis shows that RV:LV ratio measured at CTPA has a good inter-observer agreement. When the RV:LV*largest* measurement was considered as a dichotomous

categorical variable the Kappa value showed good agreement between reviewers (K:0.65, p<0.001). RV:LV assessment forms part of the echocardiographic assessment of PH, and a normal RV:LV ratio is between 0.5-0.7, with mild dilatation said to be between 0.8-1.0 (Forfia and Vachiery, 2012) and an RV:LV ratio of >1.0 is considered a sign of potential PH (Galie et al., 2016). A previous study has correlated reconstructed CTPA RV:LV ratios to those performed in echocardiography in 63 patients with acute PE(Quiroz et al., 2004). They showed a linear correlation between the reconstructed RV:LV ratio and echocardiographic RV:LV ratio of (r=0.72, p=<0.001). Our (non-reconstructed) RV:LV*largest* (r=0.61, p<0.001) showed similar results. Placement and orientation of the echocardiographic transducer directly effects RV:LV orientation and size with echocardiography being a dynamic study (Rudski et al., 2010). Echocardiography in patients with advanced lung disease can be difficult due to poor echocardiographic windows and change in cardiac orientation due to hyper-expansion form co-existent emphysema or reduction in lung volumes due to fibrosis. CT overcomes these problems (although at the expense of using ionising radiation), and multiple levels can be quickly and easily evaluated.

Our finding that RV:LV ratio at CTPA predicts mortality, whereas invasive measurement of mPAP and PVR does not is a novel finding clearly worth further study. As in the echocardiographic chapter a significant group of patients develop features of RV dysfunction although do not have PH at RHC. Perhaps it is time to reconsider if classifying PH by the same haemodynamic definition as occurs in PAH guidelines is appropriate in this group of patients who have an additional and very significant co-morbidity. Perhaps a move to assess RV function (and indeed RV dysfunction) may predict risk more appropriately and

most importantly earlier prior to the onset of PH. Therefore, I created and evaluated the RVPA interaction factor. The rational being that patients whose PH has developed gradually will have had time to develop RV compensation. This would allow time for the MPAD to dilate and while the RV is compensating the RVPA interaction factor would be <1.0. However, if an acute insult (such as an acute exacerbation / PE / rapid worsening of PH) rapidly increases PVR it may not give the RV time to adapt and RV dilatation occurs without having time for the MPAD to dilate, and the RVPA interaction factor would be ≥1.0. This theory is supported by the finding that FVC and TLco decline was greater in patients with an RVPA interaction factor ≥1.0 (p=0.03, and p=0.02 respectively) in the year preceding RHC. Although unfortunately only 69 patients of the 179 had PFT performed in the year prior to RHC for comparison which limits the findings. Additionally, PVR was significantly higher in patients with an RVPA interaction factor ≥1.0 (6.5±3.9 vs 4.4±2.1 Wood units, p<0.001), although mPAP was only marginally higher (34±8 vs 31±8mmHg, p=0.05). The approach to target patients by the presence of RV dysfunction is supported by the sub-analysis in the STEP-IPF trial (using sildenafil). Han et al showed that patients with RV dysfunction on echo had preservation of 6MWD compared to patients with RV dysfunction receiving placebo (Han et al., 2013).

The lack of ECG gating of CTPA acquisition and the fact that the images were interpreted by a Physician (with acceptable agreement between Physician and Radiologist) makes the findings of this study reproducible in everyday clinical practice.

6.5 Limitations

The main limitations of this study are its retrospective design and high prevalence of PH patients which inherently leads to bias. All patients studied: displayed clinical signs of PH, had non-invasive investigations suggesting PH or were being assessed for lung transplantation leading to a high pre-test probability of PH. Although, CTPA was performed at the time of PH assessment and therefore did not factor into the decision to refer to PH services which make findings of this study more valid. We sought to reduce bias further by studying consecutive patients and studying factors which have previously been identified to be predictive of mortality in CTPA and PAH studies. Echocardiograms were retrospectively reviewed, therefore we are unable to comment if RV:LV assessment was not possible in all the echocardiographic studies (where RV:LV ratio was not possible to report on, as the appropriate views may not have been performed as opposed to being truly unable to measure the RV and LV). Therefore, a direct comparison of CT and echocardiographic measurements was not possible. Data on lung function trends prior to RHC was limited, and there was no data relating to acute exacerbations / hospitalisations due to a respiratory cause. This data would have improved our ability to evaluate prior trends in ILD disease status and PH.

6.6 Conclusion

RV:LV ratio measured at CTPA is easy to perform with good inter-observer reproducibility and is an additional method of PH risk stratification in patients with a high clinical suspicion of PH and provides prognostic information. The presence of an RV:LV*largest* ≥1.0 or an RA

diameter ≥50mm at CTPA should strongly provoke PH investigation. Such patients even where PH is not present should be considered for referral to lung transplant services where appropriate.

Chapter 7 Prognostication in ILD-PH using baseline non-invasive parameters

7.1 Rationale

The presence of significant ILD makes the clinical detection of PH extremely challenging, although it is certain that patients with ILD-PH are at an increased risk of hospitalisation and death. It is therefore highly desirable to predict prognosis in patients with confirmed ILD-PH for the following reasons:

- To inform patient and physician of anticipated outcome.
- To guide changes in management.
- To aid in appropriate patient identification for lung-transplant evaluation, and organ allocation.
- The identification of adverse predictors may improve prediction of PH and allow new treatment avenues prior to onset of severe PH to improve outcome.
- To help promote appropriate recruitment into randomised controlled clinical trials to establish if vasodilators have a role in ILD-PH.
- Provide a platform to discuss advanced care planning.

As discussed in the introduction a wide number of studies have been performed evaluating baseline haemodynamics, and non-invasive variables, ability to predict prognosis. In general, prediction of prognosis is easier where predictors are grossly abnormal, for example an individual with an FVC of 40% predicted would be strongly anticipated to have a worse

prognosis than an individual with an FVC of 80% predicted. Although, this clear distinction rarely occurs in ILD-PH where patients with ILD and ILD-PH share similarities in PFT profiles making clear distinction of adverse thresholds extremely challenging.

In 2012 Ley et al produced a "multideminsional prognostic staging system" in IPF patients recruited for a randomised controlled clinical trials (Ley et al., 2012). The model was developed and validated using international data with a derivation cohort (n= 228, and validation cohort (n = 330). Four commonly measured variables were included in the final model: gender (G), age (A), and physiology (P) with FVC and TLco from PFT. The continuous predicotrs were converted into the GAP score and then converted to the GAP index. Three stages (Gap stage I, II, and III) were identified with 1 year mortality of 6%, 16% and 39% respectively. The GAP model performed well as a discriminator with a C-index 70.8 in the derivation and 69.3 in the validation cohort. The authors suggested that patients in GAP stage I were at a low risk of mortality and would not be ideal for mortality driven clinical trials, but could be better for symptom quality of life trials. They suggested patients in GAP stage II would be ideal for mortality driven clinical trials as up 16.2% were anticipated to die by the first year, and suggested this group should under go consideration of lung transplant. Patients in the worst GAP stage III were at a very high risk of mortality (39.2% at one year) and they suggests immediate lung transplantation consideration and palliative care (Ley et al., 2012). In 2014 Ryerson et al extended the same prognostic model to include patients with CTD-ILD, CHP, and NSIP (Ryerson et al., 2014). The original IPF GAP model was modified to predict mortality across ILDs by accounting for disease sub-type in 1208 patients. Patients with IPF and unclassifiable ILD remained with the original scoring system, however patients

with CTD-ILD, NSIP and CHP had 2 points taken away to reflect their improved prognosis. A modified ILD-GAP index was developed with risk stratified into 4 different clinical risk categories. The ILD-GAP model had good discriminative performance across all ILD subtypes (C-index 74.6 in the whole cohort). When tested in each individual ILD subtype the C-index remained >0.70 (Ryerson et al., 2014).

7.1.2 Hypothesis

I hypothesised that as in ILD, a combination of baseline non-invasive variables could be used to prognosticate in patients with confirmed ILD-PH. I also hypothesised that existing mortality prediction tools such as the ILD-GAP model would be confounded by the presence of PH.

7.2 Methods

Patients were excluded from the study if they (figure 6.1):

- Did not have pulmonary hypertension demonstrated at RHC.
- Had no PFT within six months of RHC.
- Had evidence of left heart disease following RHC and discussion at a multi-disciplinary PH meeting.

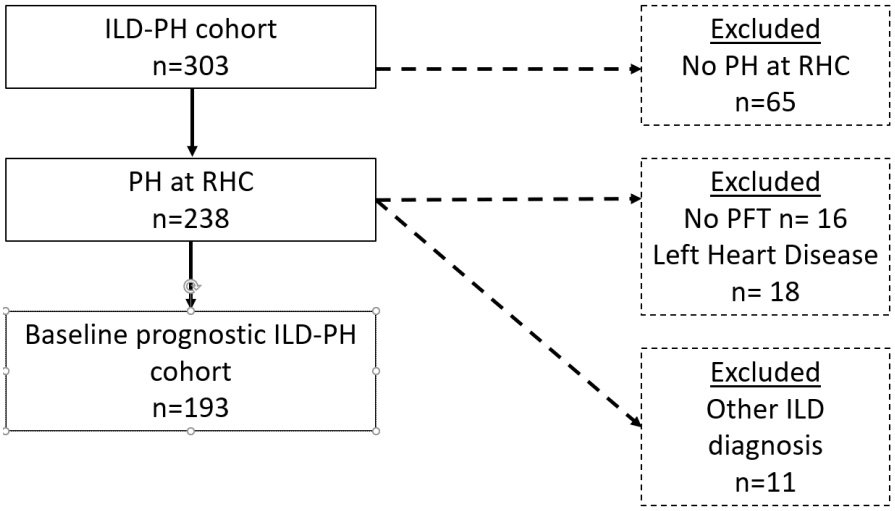


Figure 7.1. Flowchart showing the identification and exclusion of patients for baseline prognostication.

Abbreviations: ILD - Interstitial lung disease PH - Pulmonary hypertension, RHC - right heart catheter, PFT - pulmonary function testing.

Predictors of prognosis were evaluated in their ability to predict prognosis using Cox proportional hazards regression. Kaplan-Meier survival analysis was used to demonstrate estimated survival. Significant univariable predictors of mortality which remained independent predictors in multivariable analysis were used to create a prognostic score in the baseline prognostic cohort. Backward selection of variables was used, and the final multivariable model included: age at RHC, ILD diagnosis, gender, TLco (% predicted). Variables in the multivariable model which remained significant independent predictors of mortality were used to create the ILD-PH prognostic model. Age was stratified as a dichotomous categorical variable as <65 and ≥65 years of age. Thresholds of TLco were evaluated to give adequate differentiation between risk for both early and late mortality. Weighting for the threshold of each variable within the score was based upon the β

coefficient from the multivariable model (Wilson et al., 1998, Pocock et al., 2001, Hippisley-Cox et al., 2007, du Bois et al., 2011b). The β coefficient for each threshold variable was multiplied by 10 then divided by four and rounded to the nearest number. The individual scores were summed to give the ILD-PH PH prognostic score. Finally, the ILD-PH prognostic score was converted to the ILD-PH prognostic Index, to predict a low risk, mild-moderate risk and high risk of mortality. The ability of an increase in the prognostic score to predict mortality was assessed with Harrel's C-Index (Harrel's C-Index assesses the ability of a unit increase in the prognostic score to differentiate between individuals in terms of prognosis). A C-Index of ≥0.70 is considered as demonstrating that a prognostic tool/score has a good ability to identify increasing risk with an increasing score. The threshold of the ILD-PH prognostic Index was chosen to maximise the C-Index value. The cohort was split based on the median ILD severity score at CT and the ILD-PH prognostic model was tested in patients with mild-moderate ILD severity and more severe ILD. This was to ensure that the ILD-PH prognostic index performed equally as well in patients with mild-moderate ILD versus more severe ILD severity at CT. The ILD-GAP score for each patient was calculated and compared to my model. Outcome was defined as death or lung transplantation.

7.3 Results

7.3.1 Demographics and baseline invasive and non-invasive variables of the baseline ILD-PH cohort

193 patients with PH at RHC were available for prognostic analysis at baseline RHC. ILD diagnoses are shown in table 7.1, and specific CTD-ILD diagnoses (table 7.2). The mean age of the cohort was 62±11 years of age, and 51% were men (table 7.3). LTOT prescription was very high in 75% of the whole cohort. Mean pulmonary artery pressure was 37±10mmHg,

and PVR 7.4±3.8 Wood units. ILD extent was 43±14%. Mean FVC (% predicted) was 60±19%and TLCO (% predicted) 24±9%. The mean CPI was 63±11.

ILD diagnosis	Number
Connective tissue disease (CTD- ILD)	65
Idiopathic pulmonary fibrosis (IPF)	49
Sarcoidosis	44
Chronic hypersensitivity pneumonitis (CHP)	14
Non-specific interstitial pneumonitis (NSIP)	15
Unclassifiable	6
Total	193

Table 7.1. ILD diagnoses

Specific CTD-ILD diagnoses	Number
Scleroderma	24
Antisynthetase syndrome / polymyositis / Dermatomyositis	11
Undifferentiated connective tissue disease	11
Rheumatoid arthritis	8
Mixed connective tissue disease	6
Sjogren's syndrome	4
Systemic lupus erythematous	1
Total	65

Table 7.2. Connective tissue disease ILD diagnoses

ILD-PH cohort	Number of patients (n=193)
Age at right heart catheter	61±11
Gender (%, men)	51
Current smoker / Ex-smoker / Never smoker (%)	20/31/49
Long term oxygen therapy prescription (%)	75
Haemodynamics	
Mean pulmonary artery pressure (mmHg)	37±9
Cardiac output (L/m)	4.1±1.2
Pulmonary capillary wedge pressure (mmHg)	9±4
Pulmonary vascular resistance (Wood units)	7.4±3.8
CT metrics	
Extent of fibrosis (%)	44±13
Main pulmonary artery diameter (mm)	34.5±4.2
Main pulmonary artery: Aorta ratio	1.10 [1.00-1.10]
Pulmonary function tests	
Forced Expiratory $Volume_1$ (% predicted)	57±17
Forced Vital capacity (% predicted)	60±19
Gas transfer (% predicted)	24±9
Gas transfer co-efficient (% predicted)	51±15
Composite physiological index	63±11
Echocardiography	
TRv max (m/s)	3.88±0.60
Right ventricular systolic pressure (mmHg)	69±20
Right atrial area (cm^2)	21±8
RV:LV ratio (systolic, short axis view)	1.30±0.73
Fractional area change (%)	36±8
Trans annular systolic plane excursion (m/s)	18±5
Eccentricity index	1.45±0.4
Brain natriuretic peptide	
Brain natriuretic peptide (ng/L)	153 [57-447]

Table 7.3. Demographics, haemodynamics and non-invasive variables in patients with PH at RHC

Abbreviations: RV:LV - right ventricle to left ventricle ratio

7.3.2 Haemodynamics at RHC stratified by ILD diagnosis

The mPAP (p=0.2), and PVR (0.09) at RHC was not significantly different between ILD diagnostic groups (figure 7.2)

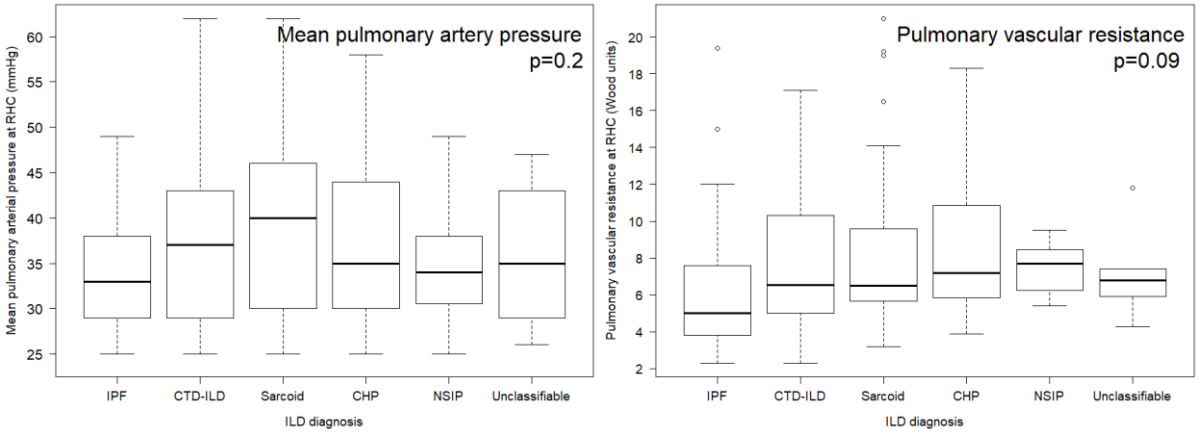


Figure 7.2. Boxplot demonstrating mean pulmonary arterial pressure and pulmonary vascular resistance measured at RHC, stratified by ILD diagnosis.

Abbreviations: IPF - Idiopathic pulmonary fibrosis, CTD-ILD - connective tissue disease associated interstitial lung disease, CHP - chronic hypersensitivity pneumonitis, NSIP - non-specific interstitial pneumonitis.

7.4 Prognostication using baseline invasive and non-invasive variables

7.4.1 Univariable assessment of mortality

Median follow up time in the prognostic ILD-PH cohort was 2.41[0.95 to 4.2 years]. 144 patients (74.6%), died or underwent lung transplantation. 134 (69.4%), patients died over the study period, and 10 (5.1%) underwent lung transplantation. The following demographic variables predicted mortality (table 7.4): age at RHC (HR 1.03, CI 1.02-1.06, p<0.001) for each year increase in age, male gender (HR 1.74, CI 1.25-2.42, p<0.001), use of LTOT (HR 1.77, CI 1.17-2.68, p=0.007). Those treated with pulmonary vasodilators (defined as

intention to treat) had a significantly better prognosis (HR 0.41, CI 0.28-0.61, p<0.001). Higher mPAP measured at RHC was associated with an improved outcome (HR 0.98, CI 0.96-0.99, p=0.02). ILD-subtype was strongly predictive of outcome, where survival was compared with CTD-ILD as the reference (most favourable outcome): IPF (HR 3.76, CI 2.44-5.80, p<0.001), unclassifiable ILD (HR 5.67, CI 2.35-13.7, p<0.001), and CHP (HR 2.30, CI 1.20-4.39, p=0.01). FVC levels at baseline predicted outcome (HR 0.98, CI 0.98-0.99, p=0.02). Measures of oxygen exchange efficiency predicted outcome: TLco (HR 0.93, CI 0.91-0.95, p<0.001), Kco (HR 0.98, CI 0.96-0.98, p<0.001), and PaO_2 (HR 0.79, CI 0.71-0.89, p<0.001). Echocardiographic variables measuring pressure performed poorly in predicting outcome. However, RV functional measurements such as RV FAC predicted outcome (HR 1.03, CI 1.00-1.05, p=0.03). An increased MPAD:Ao ratio was associated with an improved prognosis (HR 0.88, CI 0.77-1.00, p=0.05) (discussed in previous CTPA chapter 6). ILD severity measured at HRCT predicted outcome (HR 1.02, CI 1.01-1.04, p<0.001) per 1% increase in ILD severity.

	Hazard ratio	Confidence interval	P value
Demographics			
Age at right heart catheter†	1.03	1.02-1.06	<0.001
Male Gender	1.74	1.25-2.42	0.001
Long term oxygen therapy prescription	1.77	1.17-2.68	0.007
Treatment with vasodilators	0.41	0.28-0.61	<0.001
RHC Haemodynamics			
Mean pulmonary artery pressure†	0.98	0.96-0.99	0.04
Cardiac output†	0.92	0.80-1.06	0.3
Pulmonary capillary wedge pressure†	0.98	0.94-1.02	0.3
Pulmonary vascular resistance†	0.98	0.94-1.03	0.6
ILD diagnostic group			
Connective tissue disease associated ILD	-	Reference	-
Sarcoidosis	0.99	0.61-1.62	0.9
Chronic hypersensitivity pneumonitis	2.30	1.20-4.39	0.01
Idiopathic non-specific interstitial pneumonitis	1.50	0.79-2.87	0.2
Idiopathic pulmonary fibrosis	3.76	2.44-5.80	<0.001
Unclassifiable	5.67	2.35-13.7	<0.001
Pulmonary Function Tests			
Forced Expiratory Volume$_1$ (% predicted) †	1.00	0.99-1.00	0.8
Forced Vital capacity (% predicted) †	0.98	0.98-0.99	0.02
TLco (% predicted) †	0.93	0.91-0.95	<0.001
Kco (% predicted) †	0.98	0.96-0.98	<0.001
Composite physiological index†	1.05	1.03-1.07	<0.001
PaO_2 (KPa) †	0.79	0.71-0.89	<0.001
Alveolar arterial gradient	1.05	0.99-1.11	0.1
Brain Natriuretic Peptide			
BNP (Quartiles)	1.1	0.94-1.29	0.2
Echocardiography			
TRv max (m/s) †	0.94	0.72-1.24	0.7
Right ventricular systolic pressure (mmHg) †	1.00	0.99-1.01	0.8
Right atrial area (cm^2) †	1.01	0.98-1.03	0.6
RV:LV ratio†	0.87	0.65-1.16	0.3
Fractional area change (%)†	1.03	1.00-1.05	0.03
Pulmonary acceleration time	1.01	0.99-1.02	0.2
Trans annular systolic plane excursion (m/s) †	0.98	0.93-1.01	0.2
CT VARIABLES			
Main pulmonary artery diameter†	0.98	0.94-1.03	0.4
Main pulmonary artery diameter to Aorta ratio†	0.88	0.77-1.00	0.05
ILD severity †	1.02	1.01-1.04	<0.001

Table 7.4. Univariable predictors of mortality or lung transplantation performed at right heart catheterisation, predicting mortality over 6 years from RHC

Abbreviations: TLco - gas transfer, Kco - gas transfer co-efficient, TRv - max Tricuspid regurgitation maximum value, RV:LV - right ventricle to Left ventricle ratio. † As continuous variable.

7.4.2 Multivariable analysis

The strongest predictors of mortality were combined in a multivariable model, and backward stepwise removal of non-significant variables was performed. At multivariable analysis (table 7.5)**:** age, TLco (% predicted) (both expressed as continuous variables), male gender, a diagnosis of IPF, unclassifiable and CHP all remained independent predictors of mortality. All the variables also remained independent predictors once ILD severity (measured at CT) and vasodilator treatment was adjusted for (except CHP which was not an independent predictor once treatment status was accounted for). No haemodynamic, echocardiographic or CT variables remained independent predictors in the multivariable model.

	Hazard ratio	**Confidence interval**	**P value**
Multivariable model			
Age	1.03	1.01-1.05	0.001† ⊦
TLco (% predicted)	0.93	0.91-0.96	<0.001† ⊦
Male gender	1.96	1.35-2.85	<0.001† ⊦
Idiopathic pulmonary fibrosis	1.91	1.23-2.97	0.004† ⊦
Chronic hypersensitivity pneumonitis	2.00	1.05-3.84	0.04 ⊦
Unclassifiable ILD	3.19	1.21-8.39	0.02† ⊦

Table 7.5. Multivariable analysis of baseline prognostic variables.

Abbreviations: TLco gas transfer. † Remained significant following adjusting for treatment status. ⊦ Remained significant following adjusting for ILD severity measured at HRCT.

7.5 The ILD-PH TLco Score

The threshold to predict mortality for TLco and age at RHC was chosen to predict both early and late mortality (over 5 years). Kaplan-Meir survival estimates for each individual variable are shown in figure 7.3.

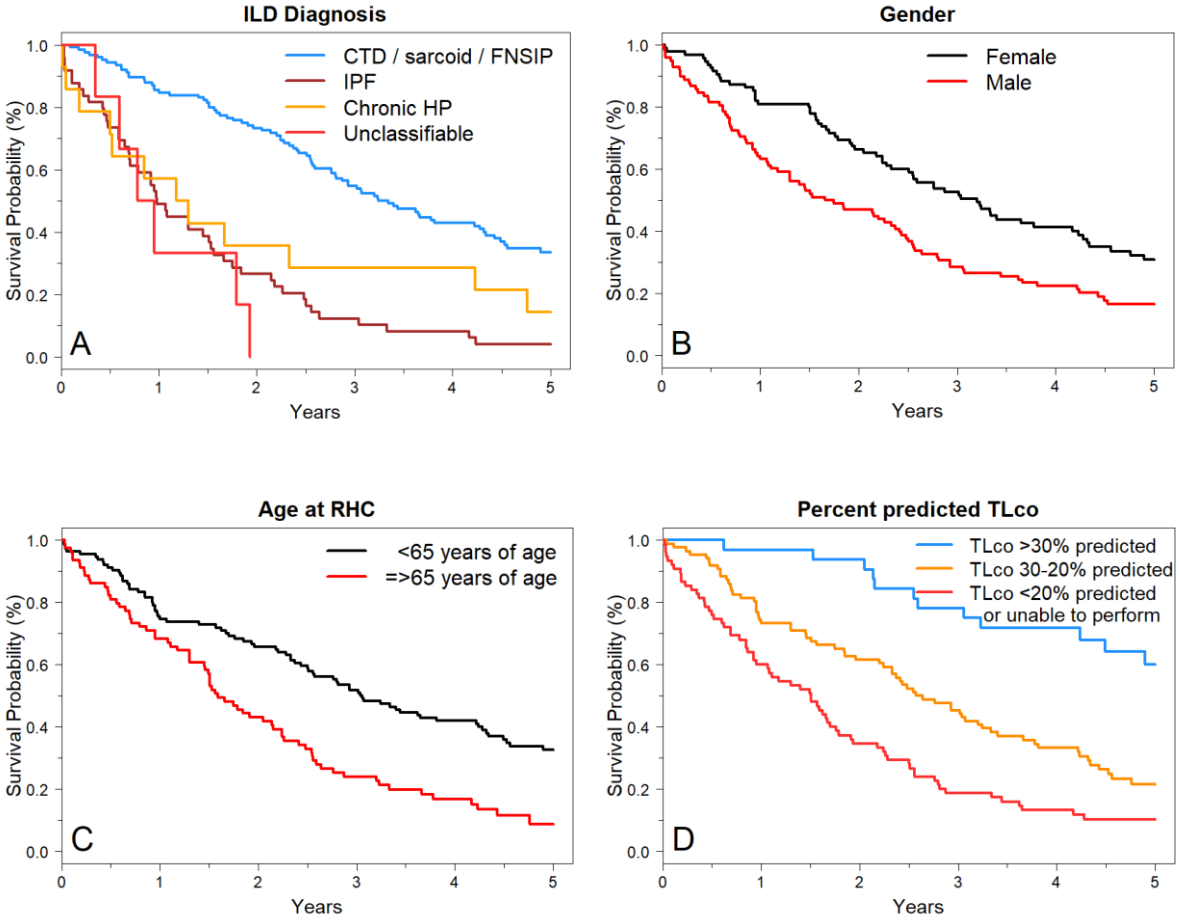


Figure 7.3. Kaplan-Meier survival estimates for each individual variable in the ILD-PH cohort.

Abbreviations: CTD - Connective tissue disease, FNSIP - Fibrotic non-specific interstitial pneumonitis, CHP - chronic hypersensitivity pneumonitis, TLco - transfer factor. Panel A - Survival estimate stratified by ILD diagnosis, Panel B - Survival estimate stratified by gender, Panel C - Survival estimate stratified by age at RHC, Panel D - Survival estimate stratified by severity of impairment in TLco (% predicted).

The hazard ratios of each dichotomous variable or threshold are shown following multivariable adjustment in table 7.6. All variables remained independent predictors of outcome in the multivariable model and remained significant following adjustment for ILD severity (at HRCT, in fact all significance levels increased), and PH treatment status (age and a diagnosis of CHP did not remain an independent predictor after adjusting for PH treatment status). The ILD-PH prognostic score is shown in table 7.7, and Kaplan-Meier plot demonstrating the score in the prognostic cohort in figure 7.3 panel A.

	Hazard ratio	Confidence Interval	P value	β coefficient	Value in score
Age ≥65	1.54	1.03-2.29	0.04 ⊦	0.429	1
Gender	1.77	1.23-2.54	0.002 ⊦	0.568	1
IPF / CHP / Unclassifiable	2.34	1.55-3.51	<0.001 ⊦	0.848	2
TLco 20-30% predicted	2.67	1.31-5.44	0.007 ⊦	0.982	2
TLco <20% predicted or unable to perform	4.81	2.34-9.87	<0.001 ⊦	1.571	4

Table 7.6. Multivariable adjustment of individual variables and thresholds in the ILD-PH prognostic index.

Abbreviations: IPF - Idiopathic pulmonary fibrosis, CHP - chronic hypersensitivity pneumonitis, TLco - gas transfer. ⊦ Remained significant following adjusting for ILD severity measured at HRCT

Variable		Points
ILD Subtype	Sarcoidosis	0
	CTD-ILD	0
	Idiopathic NSIP	0
	IPF	2
	Chronic HP	2
	Unclassifiable	2
Gender	Female	0
	Male	1
Age	<65	0
	≥65	1
TLco (% predicted)	≥31	0
	20 – 30	2
	<20 or Unable to perform	4
Score	**ILD-PH Prognostic Index**	
0 – 2		1
3 – 5		2
≥ 6		3

Table 7.7. The ILD-PH prognostic score.

Points are accumulated for each variable (range, 0-8), then converted into the ILD-PH index.

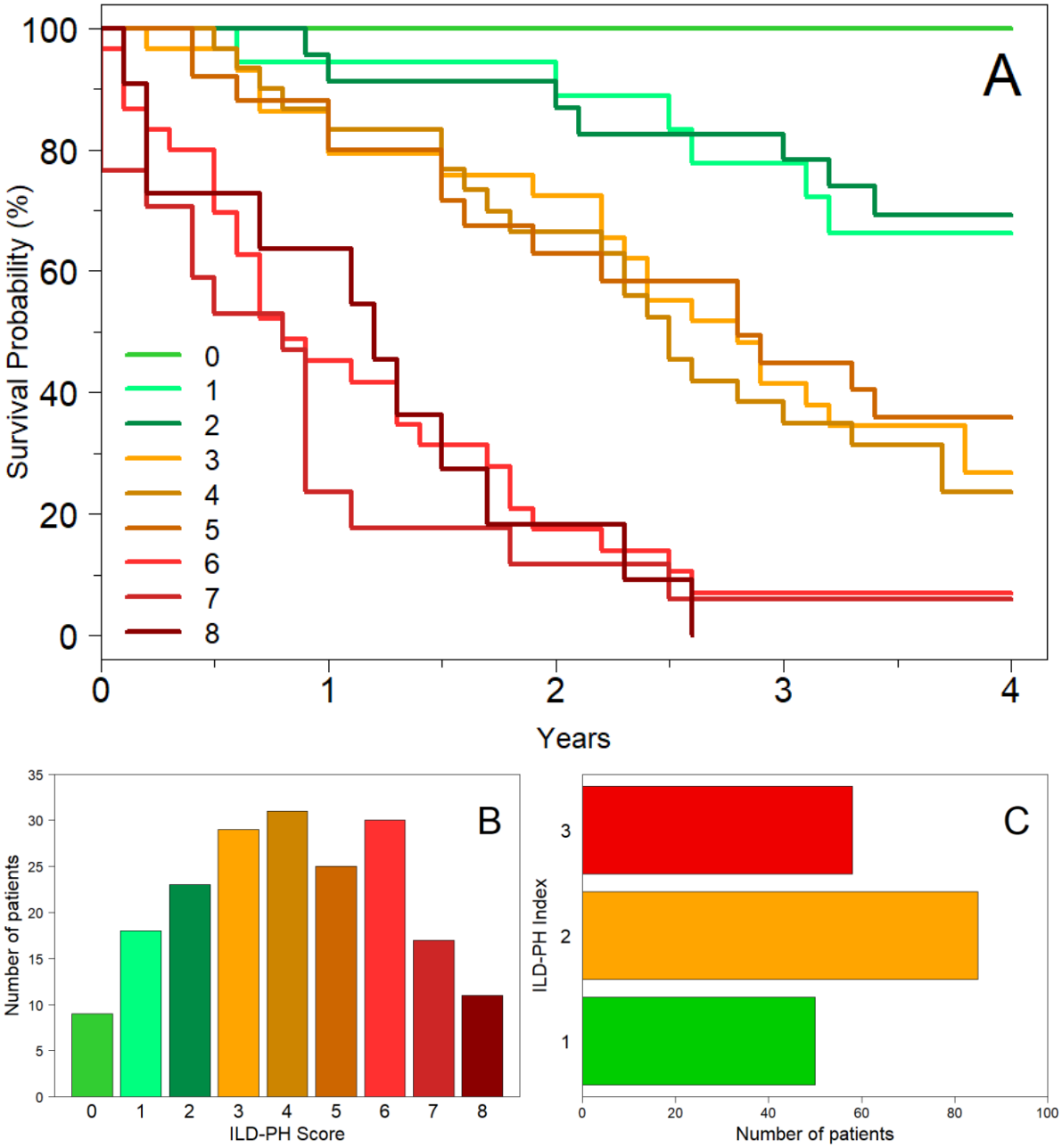
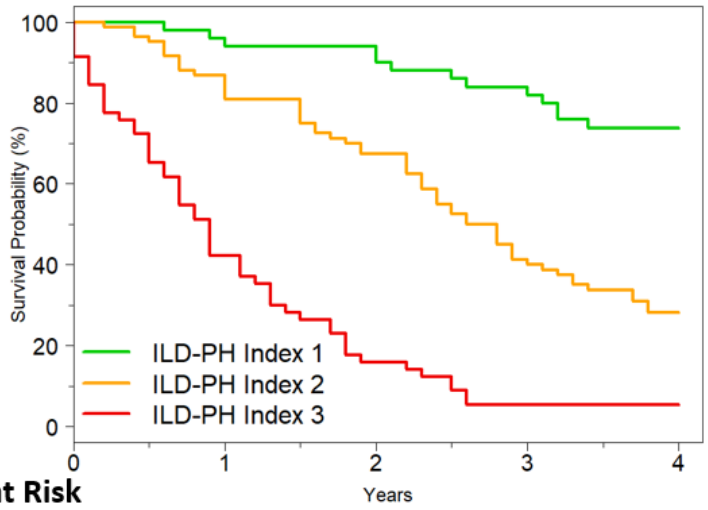


Figure 7.4. Kaplan-Meier plot demonstrating the impact of an increasing ILD-PH prognostic score, and bar charts demonstrating the distribution of the ILD-PH score and index in the ILD-PH cohort

Panel A - Kaplan-Meier survival estimates using the ILD-PH prognostic score, Panel B - Distribution of the ILD-PH prognostic score (minimum score 0, maximum score 8), Panel C - Due to similarities in clinical outcome the ILD-PH prognostic score is converted to the ILD prognostic index. Patients with an ILD-PH score of 0-2 are in ILD-PH Index 1, a score of 3-5 are in ILD-PH index 2 and patients with a score of 6-8 are in ILD-PH Index 3.

The ILD-PH score has a range of minimum score of 0, and a maximum score of 8 (figure 7.4, panel B). The ILD-PH score performs well at attributing increasing risk of death or transplant with an increasing score (C-index = 0.743). The Kaplan-Meier plot in figure 7.4 (panel A) demonstrates that the ILD-PH prognostic score can be easily differentiated into three groups based on mortality to create the ILD-PH index. A bar plot demonstrates the distribution of the ILD-PH Index is shown in figure 7.4, panel C. 50(25.9%) were stratified in ILD-PH index 1 (low risk), 85(44.0%) in ILD-PH index 2 (moderate-high risk), and 58(30.1%) were in ILD-PH Index 3 (very high risk). The Kaplan-Meier plot and number at risk table for the ILD-PH Index is shown in figure 7.5, and hazard ratios in table7.8. At 4 years of follow up the C-index for the ILD-PH Index was 0.738.



Number at Risk					
Index 1	50	47	46	42	31
Index 2	85	73	54	33	20
Index 3	58	24	9	3	3

Figure 7.5. Kaplan Meier stratified by ILD-PH index, and number at risk table.

	Number of patients	Hazard ratio	Confidence interval	p value
ILD-PH Index 1	50	Ref	Ref	Ref
ILD-PH Index 2	85	3.86	2.11-7.07	<0.001
ILD-PH Index 3	58	13.7	7.31-25.5	<0.001

Table 7.8. ILD-PH index hazard ratios for overall mortality.

7.5.2 The ILD-PH TLco Score tested in mild-moderate ILD and severe ILD

Patients in the ILD-PH prognostic cohort were split into dichotomous ILD severity groups and the ILD-PH prognostic model was tested. The score retained adequate diagnostic sensitivity in patients with mild to moderate ILD sensitivity (ILD severity 33±9%) C-Index = 0.760, and moderate to severe ILD severity (ILD severity 54±8%) C-Index = 0.721.

7.6 The ILD-GAP model tested in the ILD-PH cohort

The ILD-GAP score was calculated for each individual patient (with sarcoid patients excluded, as they were not included in the ILD-GAP analysis). The ILD-GAP score performed well as a prognostic score with a c-index of 0.711 (table 7.9). The ILD-GAP score is converted into the ILD-GAP index (c-index = 0.695). A Kaplan-Meier survival estimate plot of the ILD-GAP index is shown in figure 7.6 and hazard ratios in table 7.9.

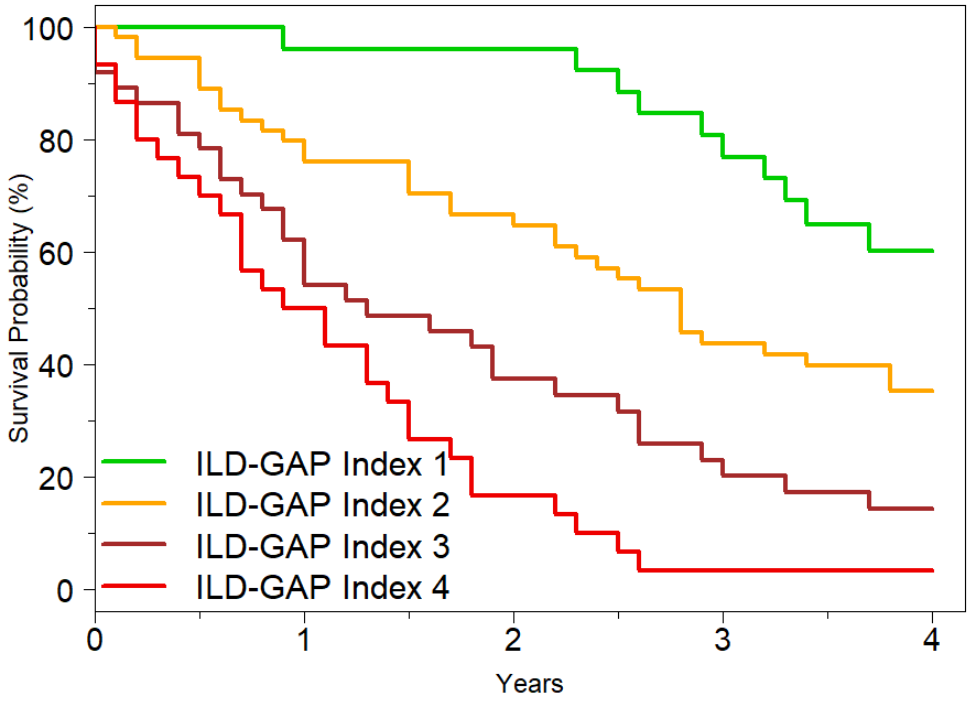


Figure 7.6. Kaplan-Meier plots showing predicted outcome using the ILD-GAP index in the ILD-PH cohort

	Number of patients	Hazard ratio	Confidence interval	P value	C-Index
ILD-GAP Score*	148	1.44	1.30-1.60	<0.001	0.711
ILD-GAP index 1	26	-	Reference	-	0.695
ILD-GAP index 2	55	2.33	1.15-4.72	0.02	-
ILD-GAP index 3	37	4.68	2.28-9.60	<0.001	-
ILD-GAP index 4	30	8.71	4.14-18.3	<0.001	-

Table 7.9. ILD-GAP score and ILD-GAP index hazard ratios from Cox proportional hazards regression.

(* As a continuous variable**)**

Mortality was much higher in ILD-PH patients compared to predicted mortality using the ILD-GAP index which reflects the much worse prognosis patients with ILD-PH experience. Mortality rates are approximately double in the ILD-PH cohort compared to those predicted by the ILD-GAP index (table 7.10).

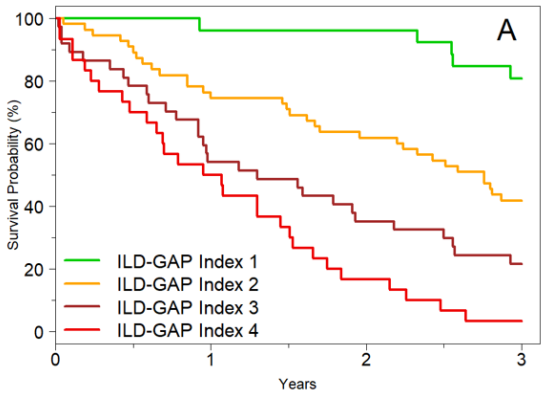
ILD-GAP Index	Predicted mortality (%)			ILD-PH cohort mortality (%)		
	1 year	2 years	3 years	1 year	2 years	3 years
ILD-GAP Index 1	3.1	6.6	10.2	3.8	3.8	19.2
ILD-GAP Index 2	8.8	18.0	26.9	25.5	38.2	58.1
ILD-GAP Index 3	18.2	35	49.2	45.9	64.9	78.3
ILD-GAP Index 4	33.5	58.4	74.8	53.3	83.3	96.7

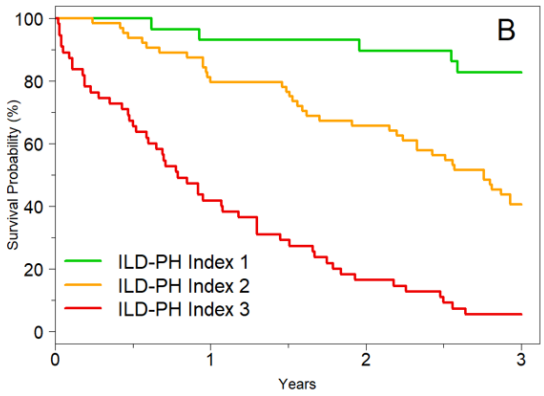
Table 7.10. Predicted and actual mortality in the ILD-PH cohort using the ILD-GAP index.

7.6.1 Comparison of the ILD-PH TLco and ILD-GAP models

Both models performed well in attributing risk of mortality when risk is either low or high (figure 7.7). However, the ILD-PH index appears to attribute risk more appropriately in the high risk patients than the ILD-GAP model. The ILD-GAP index stratified 30 (20.2%) patients in the highest risk category wheras the ILD-PH index identifed 55 (37.1%) high risk patients. Mortality in both high risk groups was exeptionally high occuring in 96.7% of the patients with the ILD-GAP model by 3 years and 94.8% in the in the ILD-PH index. Mortality was low

in both of the lowest risk categories at 3 years. The ILD-GAP model attributed 26 (17.6%) patients to the lowest risk catgory, and mortality occurred in 19.2% by 3 years. The ILD-PH index attibuted 29 (19.6%) to the lowest risk group and mortality occurred in 17.2% by 3 years. The ILD-PH index risk stratified 64 (43.2%) people as intermediate-high risk, and mortality occurred in 59.4% at 3 years.





Number at Risk				
Index 1	26	25	25	21
Index 2	55	41	34	23
Index 3	37	20	13	8
Index 4	30	14	5	1

Number at Risk				
Index 1	29	27	26	24
Index 2	64	51	42	26
Index 3	55	22	9	3

Figure 7.7. Kaplan Meier and number at risk tables for both the ILD-GAP Index and ILD-PH index

Panel A - ILD-GAP Index, Panel B - ILD-PH Index.

7.6.2 Performance of the ILD-GAP Index and ILD-PH Index with the largest ILD groups excluded

The ILD-GAP Index's C-index was 0.699 when the entire cohort was evaluated (n=148), which dropped when the major ILD diagnostic groups were excluded (table 7.11) (patients with sarcoid had already been removed as the ILD-GAP index has not been tested or validated in sarcoid patients). In-contrast, the ILD-PH CPI index was 0.730 in the whole

cohort (with sarcoid patients also removed) and retained acceptable discrimination when IPF patients were excluded. When the score was tested with CTD patients excluded (n=84) both the ILD-GAP index, and ILD-PH index dropped to <0.70, although the small number of patients is a very significant factor (table 7.11).

	Number in cohort	ILD-GAP Index	ILD-PH Index
Whole cohort	148	0.699	0.730
IPF excluded	99	0.675	0.731
CTD-ILD excluded	84	0.606	0.65

Table 7.11. Harrell's c-Index for the ILD-PH CPI Index and ILD-GAP index at 3 years of follow up, in the whole cohort and with largest ILD groups excluded.

7.7 Discussion

The ILD-PH index is the first prognostic model specifically derived in patients with RHC proven ILD associated PH. It provides a method of risk stratification in patients with RHC confirmed PH, and is more reliable across ILD subtypes than the ILD-GAP Index when PH is present. The main utilility of the ILD-PH Index would be to help guide the physician and patient to the anticipated outcome in confirmed ILD-associated PH. Patients in ILD-PH index 3 suffer a dire prognostic outlook, with 94.8% of patients in this study group experiencing mortality at 3 years. Patients in this category should (where appropriate) be urgently worked up for lung transplantation, alongside involvement of palliative care teams and advanced care planning. Mortality in the intermedate ILD-PH index group 2 is also extremely high at 59.4%. Therefore unfotunatley it seems appropriate to offer the same advice as for patients in ILD-PH Index 3. Although patients with a CTD / sarcoid associated ILD (in ILD-PH index 1) who have a good response to vasodilators and immunomodulation could be

monitered closely and re-evaluated along traditional PH and ILD pathways. Patients in the lowest risk ILD-PH group 1 experieced a 17.2% mortality at three years. Where appropriate, these patients could be closely monitered and referred for lung transplant evaluation if any further deterioration occurs or if disease severity of either ILD / PH.

The ILD-PH index could be used to screen patients for inclusion into clinical trials to evaluate vasodilators in patients with ILD-PH. As prognosis is so poor in patients with an ILD-PH index of 3, it is probable that these patients should be excluded from mortality driven studies, and if appropriate be referred for transplant assessment and palliative care. Short term mortality was extremely high in this group; 34/58(58.6%) experienced mortality at one year. Pulmonary vasodilator therapy is unlikely to improve prognosis in such a high risk group. Therefore individuals in ILD-PH index 2 would be ideal for a mortality driven study, with 20.3% in this cohort experiencing mortality within the firast year.

The finding that mortality is approximately 50% higher for a given ILD-GAP Index severity than the predicted mortality is striking and reflects the dramatically worse prognosis that patients with ILD associated PH suffer compared to patients with ILD in isolation. Ley et al (Ley et al., 2012) developed the GAP model as a multidimensional staging system in IPF using three large and distinct IPF cohorts, which was later modified and refined to predict mortality across ILD-subtypes by Ryerson et al (Ryerson et al., 2014). However, the developmement of PH confounds the use of the ILD-GAP model, and should be used with caution in patients with suspected / confirmed ILD-PH. The finding that mortality is so much worse for patients with ILD associated PH supports screening for the development of PH and the unmet clinical need for therapies to help address ILD-PH.

Interestingly, the first composite risk model to predict mortality in IPF acknowledged the fact that PH was such an adverse predictor. Watters et al derived the clinical, radiological and physiological (CRP) scoring system to predict mortality in IPF patients (Watters et al., 1986) first in 1986, and the score was then abbreviated by King et al in 2001 (King et al., 2001). The original score was derived in 183 IPF patients and included: Age, lung function, PaO2 after exercise, smoking history, the presecence of finger clubbing, extent of fibrosis and evidence of PH on chest radiograph (Watters et al., 1986).The refined score was derived prospectively in 238 patients with biopsy proven IPF (King et al., 2001). In the modification to the scoring system the presence of PH and ILD extent was given more weight as it was thought they were stronger predictors of mortality than originally thought. It is worth noting that in these patients radiographic assessment occurred by chest radiograph rather than HRCT, and that patients were treated with a combination of cylophosphamide and prednisolne, which is now accepted to shorten survivial in IPF (Idiopathic Pulmonary Fibrosis Clinical Research Network, 2012). However the score has not been externally validated and did not become widespread in its use likely because of the large number of variables required in the score. However it is intresting to note that the recogniotion of PH was included in both versions of the score. Although no future prognostic models have directly used a clinical suspicion of PH within the scoring system, those which include TLco may in part be including risk stratification for PH.

In 2002, Wells et al developed the composite physiological index (CPI) to reflect the morphological extent of pulmonary fibrosis at CT (Wells et al., 2003). Using linear regression models PFTs were fitted against CT measured severity of ILD extent. The score was derived

in 106 patients and was validated in a further 106 patitents. The CPI correlated more strongly with the extent of disease at CT than each individual PFT variable. Mortality was predicted more strongly by the CPI compared to any individual pulmonary function test (Wells et al., 2003). Du Bois et al derived a further prognostic score within a prospective cohort of 1099 IPF patients (du Bois et al., 2011b), and sought to predict mortality in IPF within one year. Independnant predictors of mortality included were: age, respiratory hospitalisation (yes or no), % predicted FVC, and 24 week change in % predicted FVC. The score predicted mortality at one year (C-statistic =0.75). The strength of Du Bois et al prognostic tool are that is encompases widely avaliable data and is easy to use, and was derived in more than 1000 IPF patients between the USA and Europe. Of note patients were recruited to the study from clinical trial cohort with mild-moderate disease and were excluded if they had significant emphysema, therefore the prevalence of PH based on studies in this cohort is probably somewhere between 10 and 20%. Despite the obvious utility of this score it has not been validated, although is widely referenced within clinical and cohort studies (Ley et al., 2016, Sharp et al., 2017).

I intended to make a prognostic model which is easy to use, the variables included are all routinely avaliable. All diagnosis or thresholds retained in the final model remained independent predictors of mortality after adjusting for ILD severity. The model has three levels of risk: ILD-PH index 1 (Low risk), ILD-PH index 2 (intermediate) and ILD-PH index 3 (high risk). Despite extremely high mortality in the cohort (62.7% at 3 years), the model was able to identify individuals with an acceptable discrimination even after the score was converted to the ILD-PH index (c-index = 0.743, when predicting mortality at three years).

The ILD-PH prognostic index remained valid when IPF patients and sarcoid patients were excluded (C-index =0.731). This demonstrates that the score is not reliant upon patients with a much more severe phenotype of disease, as it retained adequate discrimination when they were excluded. The C-index dropped to <0.70 when tested with both sarcoid and CTD patients excluded although this is likely in part due to the small number of patients in which to test the score (n=84).

It is surprising that neither haemodynamics at RHC or echocardiography did not predict mortality, indeed increasing mPAP was seen as protective in the univariable assessment of mortality (HR 0.98, CI 0.96-0.99, p=0.02, per 1mmHg increase in mPAP). There are a number of potential confounding factors:

- Patients with sarcoid and CTD-ILD (who had the best prognosis) were more likely to have greater elevations in mPAP.
- Conversly patients with IPF and unclassifiable ILD (who had the worst prognosis) had lower elevation in mPAP.
- Potential disease modifying role of pulmonary vasodilators. As discussed in chapter 3 patients were more likely to be treated if they had higher pulmonary pressures or had a diagnosis of CTD / Sarcoid. Emerging data of both retrospective review (Keir et al., 2014, Boucly et al., 2017a, Milman et al., 2008) and RCTs (Baughman et al., 2014) support the use of pulmonary vasodilators in (PDE5 inhibitors and ERAs) in sarcoid, and scleroderma (Volkmann et al., 2014).
- The indication or threshold to perform RHC is different in each ILD. For example in patients with IIP, no advanced PH therapies are recommended by ERS/ESC

guidelines (Galiè et al., 2015). PH services have been unable to prescribe advanced therapies in IIP associated PH. Therefore the threshold to perform RHC in IIP patients is much higher. Therefore RHC procedures were not pursued unless PH wa thought to be severe. This lead time bias is likely to have impacted on the prognosis of patients with IIP, again diluting the true effect of PH.

The two strongest predictors in the model were ILD diagnosis and TLco (% predicted). CHP also remained an adverse predictor following multivariable adjustment. A sub-group of patients with CHP have been noted to follow an IPF like disease process; factors linked to: extensive fibrosis (Mooney et al., 2013), pulmonary vessel volume (Jacob et al., 2017a), and signs of PH at echocardiography (Koschel et al., 2012).

Unlike in the ILD-GAP model, FVC was not a univariable or independent multivariable predictor of mortality. We did not demonstrate any correlation of FVC with mPAP in our cohort, and no clear asociation with the degree of fibrosis (Zisman et al., 2007a) or pulmonary function tests (Lettieri et al., 2006) has been found previously. TLco is commonly reduced in PAH patieants (Galiè et al., 2015). In PAH severely reduced TLco levels (<45% predicted) are associated with a poor outcome (Sun et al., 2003, Trip et al., 2013).

7.8 Limitations

The single centre, retrospective nature of the study is clearly a strong limitation, and the prognostic score requires testing and validation in an additional external cohort of patients, before it can be endorsed for use. The strength of the ILD-PH index (the fact it was derived in a population with PH confirmed at RHC) is also a limitation for its generalised usage. The

number of diagnostic RHC procedures carried out in ILD patients are unlikely to increase in the future (unless benefit of treating PH associated ILD can be demonstrated) therefore the population which this applies to is small. Although it is very useful in risk stratifying patients referred for lung transplant evaluation as RHC is mandatory if PH is suspected.

The ILD-PH index was derived in a group of patients with heterogeneous ILDs; therefore, it was not possible to adjust for ILD treatment in this analysis. Also, this is a relatively historic cohort of patients prior to widespread usage of antifibrotics which may impact on its use in IPF patients on antifibrotics. It was also not possible to adjust for the use of advanced therapies for PH, as there was a broad range of advanced therapies prescribed (single and combination therapy).

7.9 Conclusion

This chapter has confirmed that ILD-PH patients experience a worse prognosis than patients with ILD of the same severity. This reinforces efforts to understand why some patients with ILD develop PH, and whether this process can be prevented from developing or treated once PH is established. The ILD-PH prognostic score provides a framework for severity assessment prior to recruitment to event driven randomised controlled clinical trials or for lung transplant assessment. It is worth noting that 30 patients within the ILD-PH prognostic cohort were included in the BPHIT trial, 12/30(60%) were stratified in ILD PH index 3. The poor prognosis of patients within the study group may explain why no benefit was seen in terms of mortality.

Chapter 8 Prognostication in ILD-PH using longitudinal trends in non-invasive parameters

8.1 Rationale for study

Prognostication using longitudinal change in pulmonary function tests (Zappala et al., 2010, Flaherty et al., 2003, Collard et al., 2003, du Bois et al., 2011b, Richeldi et al., 2012) has been shown to be a valid method of predicting mortality in ILD and is a cornerstone of monitoring disease progression and response to therapy (Raghu et al., 2015). Often patients with ILD-PH have severely reduced pulmonary function tests (particularly gas transfer and gas transfer co-efficient). Therefore, it is highly likely that deterioration in an already severely reduced predictor will provide greater insight into longitudinal disease trends compared to cross-sectional measurement at baseline. Patients with ILD-PH have parenchymal fibrosis, and pulmonary vascular limitation. It is likely that a patient with ILD-PH will respond to an acute worsening in ILD or PH more severely than a patient with preserved pulmonary vasculature and RV function. Therefore, a small deterioration in ILD or PH is likely to have a greater effect in patients with co-existent ILD-PH.

ILD has is a heterogeneous disease course, with some patients deteriorating rapidly, some a stepwise deterioration, some a slow progressive deterioration, and a small number showing minimal deterioration (Johannson et al., 2015). Many clinical models of disease behaviour have been generated in ILD. As discussed previously many clinical risk models have been produced in IPF (Watters et al., 1986, Wells et al., 2003, du Bois et al., 2011b, Ley et al., 2012) and some have been modified to include patients with other forms of ILD (Ryerson et

al., 2014). Recently the original du Bois and GAP models have been combined to include both baseline disease severity assessments with modification for longitudinal disease behaviour (Ley et al., 2015). This was performed in 1109 patients with mild to moderate IPF from patients enlisted from clinical trials. The original GAP model overestimated mortality risk particularly in the low to moderate risk groups, with most of the model's power coming from PFT characteristics, rather than age and gender. The original model was "re-fit", with the significance of an age >65, and the more severely reduced lung function variables increasing within the score. The original model achieved a C-statistic of 0.676; following the "re-fit", the C-statistic increased to 0.757. Individual variables that significantly improved the discriminative performance, when added to the GAP model (assessed by change in the C-statistic), were occurrence of a respiratory hospitalisation and 24week change in FVC. The addition of the occurrence of a respiratory hospitalisation and 24-week change in FVC improved the C-statistic by 0.023, and reassigned patients in the intermediate risk to higher or lower risk groups.

8.1.2 Hypothesis

I hypothesised that the ILD-PH prognostic index would continue to prognosticate when re-calculated over follow up and that the addition of longitudinal disease behaviour would improve the discrimination of the score.

8.2 Methods

To be eligible for longitudinal analysis, patients had to have the baseline non-invasive variable of interest performed at the time of the RHC, and have the non-invasive variable repeated between 3 months and 15 months after the RHC (figure 8.1).

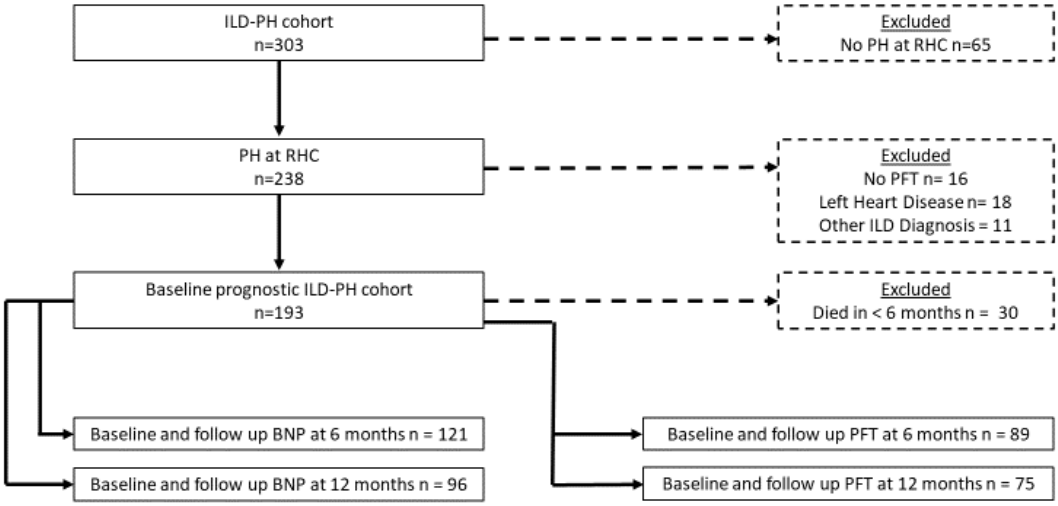


Figure 8.1. Patient selection for longitudinal analysis

Flow chart demonstrating patient inclusion and exclusion criteria for the longitudinal mortality evaluation.

Individual linear regression lines were created for each individual patient in order to standardise the time of repeat testing and determine follow up time (Schmidt et al., 2011) (figure 8.2). For example, if a patient had a PFT performed at month 5, and 7 then both sets of pulmonary function test were included along with the baseline value and linear regression was performed in order to estimate the value of the non-invasive investigation at 6 months. This was performed to standardise follow up times as the start of follow up for survival analysis. Follow up was standardised to 6, and 12 months post RHC.

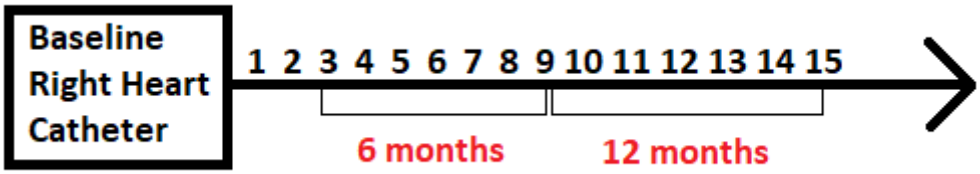


Figure 8.2. Longitudinal analysis

Patients were included in the longitudinal cohort if they had the investigation performed at the time of the RHC, and again at least once between 3 and 15 months following the RHC. Individual regression lines were created for each follow up period including all non-invasive investigations tests performed within that follow-up period. Follow-up was standardised to 6, and 12 months after RHC.

Relative change in PFT variables was calculated as [interval value - baseline value ÷ baseline value x 100]. A significant decline in FVC, was defined as ≥10%, or >5%. A significant decline in TLco and Kco was defined a relative decline of ≥15%. Patients who were unable to complete the PFT due to an inability to complete the test due to exhaustion / inability to breath hold for the gas transfer were also included and analysed separately. Logistic regression was used to assess if patients with IPF/CHP/unclassifiable ILD were more likely to experience a decline in PFT than patients with sarcoid / CTD and NSIP. The multivariable model was adjusted for age, gender, and ILD extent at HRCT.

As BNP is non-normally distributed, the raw data was transformed to the natural logarithm before undergoing linear regression techniques and then was transformed back to normal data prior to further analysis. Again, as BNP is not normally distributed, BNP was investigated in quartiles based upon its distribution within the study group. BNP quartiles were evaluated at the following level (normal BNP <20ng/L), 0-57ng/L, 58-134ng/L, 135-296ng/L and ≥297ng/L. BNP was also evaluated in terms of whether it was increasing or

decreasing from its baseline value when performed at the RHC. The rate of change in the BNP was calculated as [interval value - baseline value ÷ by the time in months from the baseline test]. A significant increase in BNP was defined as a rate of change of >2ng/L at 6 months (which was equivalent to an increase in BNP of 12ng/L), and >1ng/L at 12 months (again equivalent to an increase in BNP of 12ng/L).

The ILD-PH prognostic score previously described in chapter 6 was recalculated at 6, and 12 months post RHC, using the PFT values obtained by linear regression. Univariable Cox proportional hazards was performed for all-cause mortality and lung transplantation using longitudinal change in PFT variables and BNP values. Multivariable analysis adjusted for baseline PFT/BNP values, ILD diagnosis, use of LTOT, age and gender were performed. The longitudinal ILD-PH prognostic score was created by integrating significant longitudinal predictors of mortality based on the β coefficient (Wilson et al., 1998, Pocock et al., 2001, Hippisley-Cox et al., 2007). A new model which utilised only significant predictors at 6 and 12 months was created based upon their β coefficient, and the gas transfer threshold was "re-fitted". Model discrimination was assessed using the C-index. Follow-up time was from the date of the follow up investigation at either 6 or 12 months, until either the primary outcome occurred, or the patients were censored at the last point of clinical contact.

8.3 Results

8.3.1 The ILD-PH Score recalculated 6 months post RHC

The ILD-PH score was recalculated in 89 patients who had follow-up pulmonary function tests available at 6 months post RHC. The ILD-PH index remained the same as at baseline

RHC in n=75 (84%) of the cohort. The ILD-PH Index increased in n=6 (7%) and decreased in n=8 (9% of the cohort).

8.3.2 Univariable analysis of the ILD-PH score at six months

At univariable analysis (Table 8.1), all the individual variables within the ILD-PH prognostic index predicted mortality, apart from being over 65 years of age (HR 1.67, CI 0.94-2.96, p=0.08). Kaplan-Meir survival estimates for each variable are shown in figure 8.3.

	Hazard ratio	Confidence Interval	P value
Age ≥65	1.67	0.94-2.96	0.08
Gender	1.91	1.13-3.23	0.02
IPF / CHP / Unclassifiable	1.62	1.24-2.12	<0.001
TLco 20-30% predicted	4.05	1.20-13.7	0.02
TLco <20% predicted or unable to perform	13.3	4.05-43.8	<0.001

Table 8.1. Univariable predictors of mortality or lung transplantation performed six months post right heart catheterisation

Abbreviations: TLco - gas transfer, IPF - Idiopathic pulmonary fibrosis, CHP - chronic hypersensitivity pneumonitis, TLco - transfer factor.

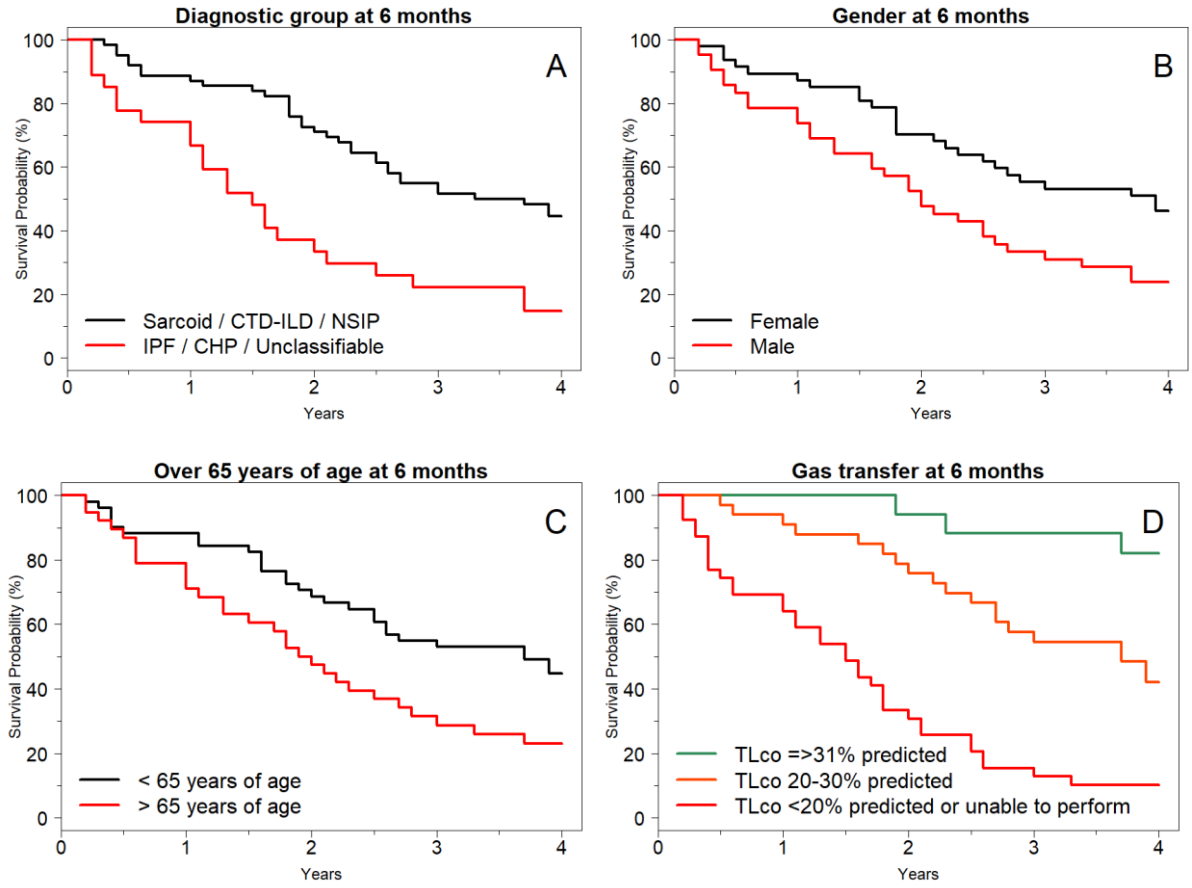


Figure 8.3. Kaplan-Meier survival estimates for each individual variable in the ILD-PH cohort, recalculated at 6 months post RHC.

Abbreviations: CTD - Connective tissue disease, NSIP - non-specific interstitial pneumonitis, IPF - Idiopathic pulmonary fibrosis, CHP - chronic hypersensitivity pneumonitis, TLco - transfer factor Panel A - Survival estimate stratified by ILD diagnosis, Panel B - Survival estimate stratified by gender, Panel C - Survival estimate stratified by age at RHC, Panel D - Survival estimate stratified by severity of impairment in TLco (% predicted).

8.3.3 Multivariable analysis of the ILD-PH score at six months

When the ILD-PH score was recalculated in a multivariable setting only ILD diagnosis (HR 2.16, CI 1.19-3.94, p=0.01), and a severely reduced TLco <20% (HR 10.9, CI 3.21-36.88, p<0.001), remained independent predictors of mortality (Table 8.2).

	Hazard ratio	Confidence Interval	P value
Age ≥65	1.22	0.69-2.15	0.5
Gender	1.14	0.65-2.09	0.7
IPF / CHP / Unclassifiable	2.16	1.19-3.94	0.01
TLco 20-30% predicted	3.21	0.93-11.0	0.06
TLco <20% predicted or unable to perform	10.9	3.21-36.8	<0.001

Table 8.2. Multivariable predictors of mortality or lung transplantation performed six months post right heart catheterisation

Abbreviations: As per table 8.1.

Kaplan-Meier survival estimates for the ILD-PH index are shown in figure 8.4. An ILD-PH index of 2 was associated with a significantly worse prognosis than an ILD-PH index 1 (HR 5.74, CI 2.22-14.8, p<0.001) (table 8.3). An ILD-PH index of 3 was associated with a severely reduced prognosis compared to an ILD-PH index 1 (HR 15.3, CI 5.67-41.5, p<0.001). The C-index for the discrimination of the ILD-PH Index recalculated at 6 months was 0.726.

	Number of patients	Hazard ratio	Confidence interval	p value
ILD-PH Index 1	25	Ref	Ref	Ref
ILD-PH Index 2	41	5.74	2.22-14.8	<0.001
ILD-PH Index 3	23	15.3	5.67-41.5	<0.001

Table 8.3. Cox analysis for the ILD-PH index at six months

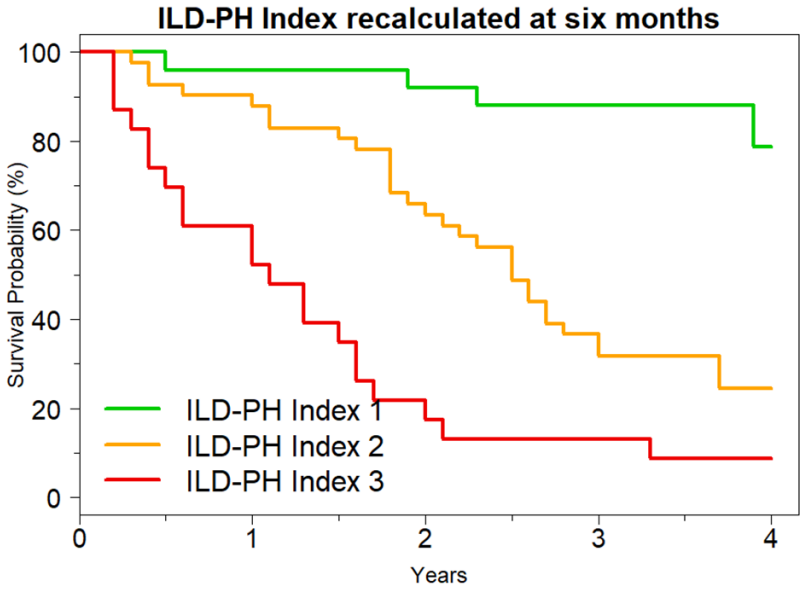


Figure 8.4. Kaplan-Meier survival estimates for the ILD-PH index recalculated at six months.

8.3.4 The ILD-PH Score recalculated twelve months post RHC

The ILD-PH score was recalculated in 75 patients who had follow up pulmonary function tests available at 12 months post RHC. The ILD-PH index remained the same as at baseline RHC in n=63 (84%) of the cohort. The ILD-PH Index increased in n=7 (9%) and decreased in n=5 (7% of the cohort).

8.3.4.1 Univariable analysis of the ILD-PH score at twelve months

At univariable analysis (Table 8.4), all the individual variables within the ILD-PH prognostic index predicted mortality, apart from gender (HR 1.75, CI 0.96-3.19, p=0.07). Kaplan-Meir survival estimates for each individual variable are shown in figure 8.5.

	Hazard ratio	Confidence Interval	P value
Age ≥65	2.18	1.05-4.53	0.04
Gender	1.75	0.96-3.19	0.07
IPF / CHP / Unclassifiable	3.95	2.06-7.58	<0.001
TLco 20-30% predicted	3.70	1.08-12.7	0.04
TLco <20% predicted or unable to perform	9.45	2.83-31.6	<0.001

Table 8.4. Univariable predictors of mortality or lung transplantation performed twelve months post right heart catheterisation

Abbreviations: As per table 8.1.

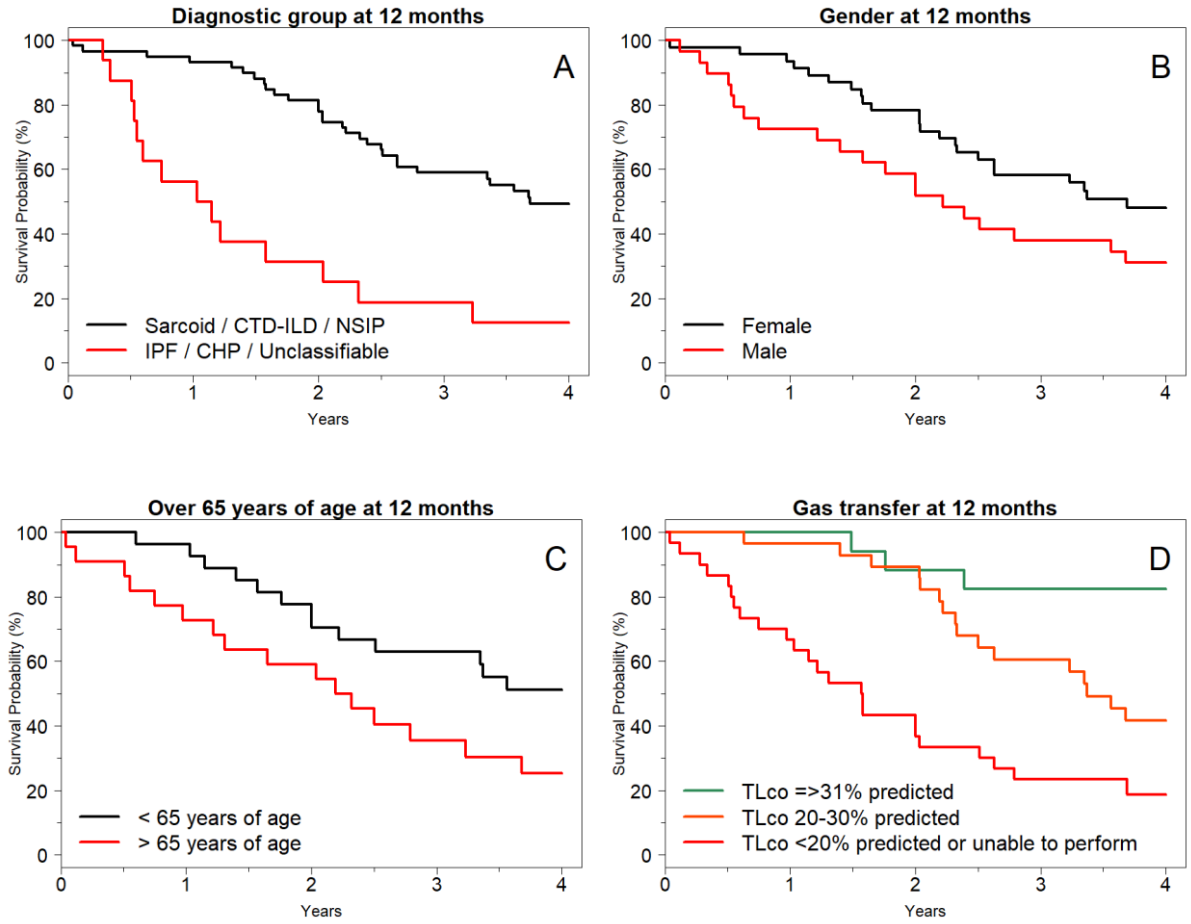


Figure 8.5. Kaplan-Meier survival estimates for each individual variable in the ILD-PH cohort, recalculated at 12 months post RHC.

Panel A - Survival estimate stratified by ILD diagnosis, Panel B - Survival estimate stratified by gender, Panel C - Survival estimate stratified by age at RHC, Panel D - Survival estimate stratified by severity of impairment in TLco (% predicted). Abbreviations: CTD Connective tissue disease, FNSIP Fibrotic non-specific interstitial pneumonitis, otherwise as table 8.1.

8.3.4.3 Multivariable analysis of the ILD-PH score at twelve months

When the ILD-PH score was recalculated in a multivariable setting age over 65 (HR 2.23, CI 1.07-4.63, p=0.03), ILD diagnosis (HR 3.44, CI 1.59-7.44, p=0.02), and a severely reduced TLco <20% (HR 8.0., CI 2.34-27.6, p<0.001), remained independent predictors of mortality (Table 8.5).

	Hazard ratio	Confidence Interval	P value
Age ≥65	2.23	1.07-4.63	0.03
Gender	1.61	0.81-3.24	0.2
IPF / CHP / Unclassifiable	3.44	1.59-7.44	0.002
TLco 20-30% predicted	2.11	0.57-7.79	0.3
TLco <20% predicted or unable to perform	8.03	2.34-27.6	<0.001

Table 8.5. Multivariable predictors of mortality or lung transplantation performed twelve months post right heart catheterisation

Abbreviations: As per table 8.1.

Kaplan-Meier survival estimates for the ILD-PH index are shown in figure 8.6. An ILD-PH index of 2 was associated with a significantly worse prognosis than an ILD-PH index 1 (HR 3.22, CI 1.37-7.55, p=0.007) (table 8.6). An ILD-PH index of 3 was associated with a severely reduced prognosis compared to an ILD-PH index 1 (HR 23.8, CI 8.91-63.7, p<0.001). The C-index for the discrimination of the ILD-PH Index recalculated at 12 months was 0.737.

	Number of patients	Hazard ratio	Confidence interval	p value
ILD-PH Index 1	26	Ref	Ref	Ref
ILD-PH Index 2	35	3.22	1.37-7.55	0.007
ILD-PH Index 3	14	23.8	8.91-63.7	<0.001

Table 8.6. Cox analysis for the ILD-PH index at twelve months

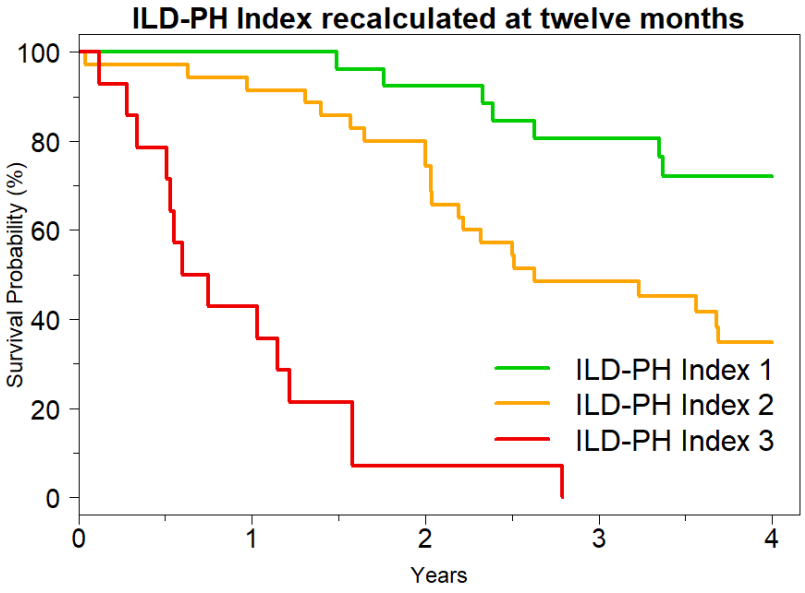


Figure 8.6. Kaplan-Meier survival estimates for the ILD-PH index recalculated at twelve months

8.3.5 Longitudinal change in Pulmonary function tests six months post RHC.

8.3.5.1 Baseline characteristics of the cohort with PFT available at six months

89 patients had repeat pulmonary function tests available for analysis six months post RHC. The ILD diagnoses for this group are shown in table 8.7. Patients with CTD-ILD (n=35, 39%), IPF (n=21, 24%) and sarcoid (n=21, 24%) made up most of the group.

ILD diagnosis	Number
Connective tissue disease	35
Idiopathic pulmonary fibrosis	21
Sarcoidosis	21
Chronic hypersensitivity pneumonitis	5
Non-specific interstitial pneumonitis	6
Unclassifiable	1
Total	89

Table 8.7. ILD Diagnoses of the patients with available follow PFT at six months

The average age was 61±11 years, and 47% were men (Table 8.8). The mean MPAP (at baseline) was 38±10mmHg, and PVR was 7.4±4.0 Wood units. The mean extent of fibrosis at CT was 44±12%.

ILD-PH Longitudinal cohort	Number of patients (n=89)
Age at right heart catheter	61±11
Gender (%, men)	47
Long term oxygen therapy prescription (%)	76
Haemodynamics (at baseline)	
Mean pulmonary artery pressure (mmHg)	38±10
Cardiac output (L/m)	4.1±1.2
Pulmonary capillary wedge pressure (mmHg)	10±4
Pulmonary vascular resistance (Wood units)	7.4±4.0
CT metrics (at baseline)	
Extent of fibrosis (%)	44±12
Pulmonary function tests	
Forced Expiratory Volume$_1$ (% predicted)	58±15
Forced Vital capacity (% predicted)	61±16
Gas transfer (% predicted)	24±8
Gas transfer co-efficient (% predicted)	50±14

Table 8.8. Baseline demographics of the patients with available follow up PFT's at six months.

8.3.5.2 Frequency of PFT decline and univariable assessment of mortality / lung transplant at six months post RHC

Decline in FVC of 5-10% was common occurring in n=26 (29%) of the cohort and associated with an adverse outcome, HR:2.26 (CI:1.18-4.33, p=0.01) (Table 8.9, and figure 8.7 panel A). The inability to perform the FVC manoeuvre was a very poor prognostic sign, HR:7.20 (CI:2.06-25.2, p=0.002). A ≥15% decline in TLco was a poor prognostic marker, HR:4.81 (CI:2.58-8.96, p<0.001) (figure 8.7 panel B). Similarly, a ≥15% decline in Kco was a poor prognostic marker, HR:7.80 (CI:3.80-16.0, p<0.001) (figure 8.7 panel C). The inability to perform TLco/Kco was a very poor prognostic marker, HR:8.06 (CI:2.62-18.0, p<0.001).

	Decline in Pulmonary function tests at 6 months			
	6 months decline in Forced vital capacity			
	≥5%	**≥10%**	**≥15%**	**Unable**
Frequency Number (%)	26 (29)	11 (12)	7 (8)	3 (3)
Cox analysis HR (CI)	2.26 (1.18-4.33)	1.07 (0.26-4.46)	2.67 (1.11-6.40)	7.20 (2.06-25.2)
	6 months decline in Gas transfer			
	≥5%	**≥10%**	**≥15%**	**Unable**
Frequency Number (%)	27 (30)	21 (24)	19 (21)	10 (11)
Cox analysis HR (CI)	2.02 (0.70-5.81)	-	4.81 (2.58-8.96)	7.58 (2.58-8.96)
	6 months decline in gas transfer co-efficient			
	≥5%	**≥10%**	**≥15%**	**Unable**
Frequency Number (%)	35 (39)	23 (26)	14 (16)	10 (11)
Cox analysis HR (CI)	1.57 (0.70-3.60)	1.27 (0.48-3.38)	7.80 (3.80-16.0)	8.06 (3.62-18.0)

Table 8.9. Frequency of decline in pulmonary function tests six months post RHC, and hazard ratios using univariable Cox analysis.

Abbreviations: HR Hazard Ratio, CI - Confidence Interval. (No results available for ≥10% decline in TLco as no one experienced mortality from this group during follow up.)

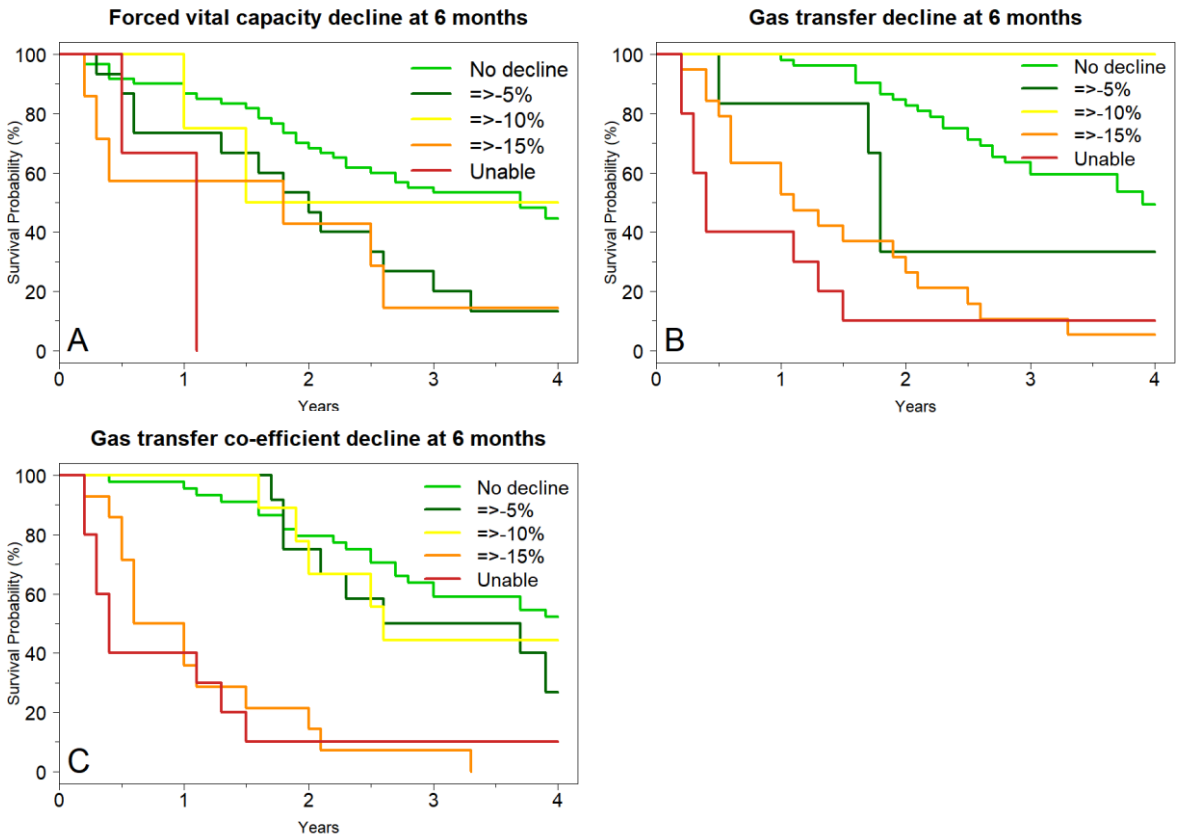


Figure 8.7. Kaplan-Meier survival estimates for decline in pulmonary function test six months post right heart catheterisation.

Panel A - decline in FVC, Panel B - decline in gas transfer, Panel C - decline in gas-transfer co-efficient

8.3.5.3 Multivariable assessment of outcome using longitudinal PFT changes at six months post RHC

Multivariable adjustment included ILD diagnosis, gender, age, ILD score at CT, and baseline PFT. A 5% decline in FVC (or the inability to complete the test) remained an independent predictor of mortality or lung transplant, HR:2.21 (CI:1.24-3.91, p=0.007) (Table 8.10). A 15% decline in TLco (or the inability to complete the test) also remained an independent predictor after multivariable adjustment, HR:4.82 (CI:2.25-10.3, p<0.001), as did Kco, HR:8.55 (CI:3.67-19.9, p<0.001).

	HR (95% CI)	Adjusted HR (95% CI) ≠
6 months decline in FVC of ≥5%	2.30 (1.35-3.92)	2.21 (1.25-3.91)
6 months decline in TLco of ≥15%	5.30 (3.08-9.13)	4.82 (2.25-10.3)
6 months decline in Kco of ≥15%	6.95 (3.94-12.3)	8.55 (3.67-19.9)

Table 8.10. Univariable and multivariable Cox analysis for PFT decline six months post RHC.

Abbreviations: HR - Hazard Ratio, CI - Confidence Interval, FVC - Forced vital capacity, TLco - Gas transfer, Kco - Gas transfer co-efficient. ≠ Adjusted for; ILD diagnosis, gender, age, ILD score at CT, baseline PFT of interest, and follow up PFT. The above multivariable analysis consists of three different models. For example, in the case FVC the model included; ILD diagnosis, gender, age, ILD score at CT, baseline FVC and 6 months decline in FVC.

8.3.6 Baseline characteristics of the cohort with PFT available at twelve months

75 patients had repeat pulmonary function tests available for analysis twelve months post RHC. The ILD diagnoses for this group are shown in table 8.11. Patients with CTD-ILD (n=32, 43%), IPF (n=10, 13%) and sarcoid (n=20, 27%) again made up most of the group.

ILD diagnosis	Number
Connective tissue disease	32
Idiopathic pulmonary fibrosis	10
Sarcoidosis	20
Chronic hypersensitivity pneumonitis	5
Non-specific interstitial pneumonitis	7
Unclassifiable	1
Total	75

Table 8.11. ILD Diagnoses of the patients with available follow PFT at twelve months

The average age of the cohort with available follow up PFT at twelve months was 59±12 (Table 8.12), and 39% were male. The mean PAP was 38±9mmHg, and mean PVR was 9.9±4.0 Wood units. The mean extent of fibrosis at CT was 42±14%.

ILD-PH Longitudinal cohort	Number of patients (n=77)
Age at right heart catheter	59±12
Gender (%, men)	39
Long term oxygen therapy prescription (%)	73
Haemodynamics (at baseline)	
Mean pulmonary artery pressure (mmHg)	38±9
Cardiac output (L/m)	4.4±1.2
Pulmonary capillary wedge pressure (mmHg)	10±4
Pulmonary vascular resistance (Wood units)	9.9±4.0
CT metrics (at baseline)	
Extent of fibrosis (%)	42±14
Pulmonary function tests	
Forced Expiratory Volume$_1$ (% predicted)	59±18
Forced Vital capacity (% predicted)	62±17
Gas transfer (% predicted)	26±10
Gas transfer co-efficient (% predicted)	53±15

Table 8.12. Baseline demographics of the patients with available follow up PFT's at twelve months.

8.3.6.1 Frequency of PFT decline and univariable assessment of mortality / lung transplant at twelve months post RHC

Decline in FVC of ≥5-10%, was common occurring in n=25 (32%) of the cohort, but unlike at six months was not associated with an adverse outcome, HR:2.10 (CI:0.94-4.70, p=0.07) (Table 8.13, and figure 8.8 panel A). The inability to perform the FVC manoeuvre was less frequent than at six months and was not an adverse prognostic sign, HR:1.37 (CI:0.09-5.43, p=0.8). A ≥15% decline in TLco occurred in n=19(25%) and was a poor prognostic marker, HR:3.95 (CI:1.94-8.04, p<0.001) (figure 8.8, panel B). Similarly, a ≥15% decline in Kco (which occurred in n=15(19%)) was a poor prognostic marker, HR:2.95 (CI:1.44-6.05, p=0.003) (figure 8.8 panel C). The inability to perform TLco/Kco was again a very poor prognostic marker, HR:29.5 (CI:7.63-114.0, p<0.001).

	Decline in Pulmonary function tests at 12 months			
	12 months decline in Forced vital capacity			
	≥5%	**≥10%**	**≥15%**	**Unable**
Frequency Number (%)	25 (32)	15 (19)	10 (13)	3 (4)
Cox analysis HR (CI)	2.10 (0.94-4.70)	3.63 (1.24-10.6)	1.41 (0.59-3.54)	1.37 (0.09-5.43)
	12 months decline in Gas transfer			
	≥5%	**≥10%**	**≥15%**	**Unable**
Frequency Number (%)	40 (52)	33 (43)	19 (25)	4 (5)
Cox analysis HR (CI)	1.19 (0.34-4.12)	1.49 (0.54-4.11)	3.95 (1.94-8.04)	40.0 (10.0-160)
	12 months decline in gas transfer co-efficient			
	≥5%	**≥10%**	**≥15%**	**Unable**
Frequency Number (%)	31 (40)	24 (31)	15 (19)	4 (19)
Cox analysis HR (CI)	1.55 (0.58-4.14)	0.35 (0.08-1.48)	2.95 (1.44-6.05)	29.5 (7.63-114)

Table 8.13. Frequency of decline in pulmonary function tests twelve months post RHC, and hazard ratios using univariable Cox analysis.

Abbreviations: As per table 8.9.

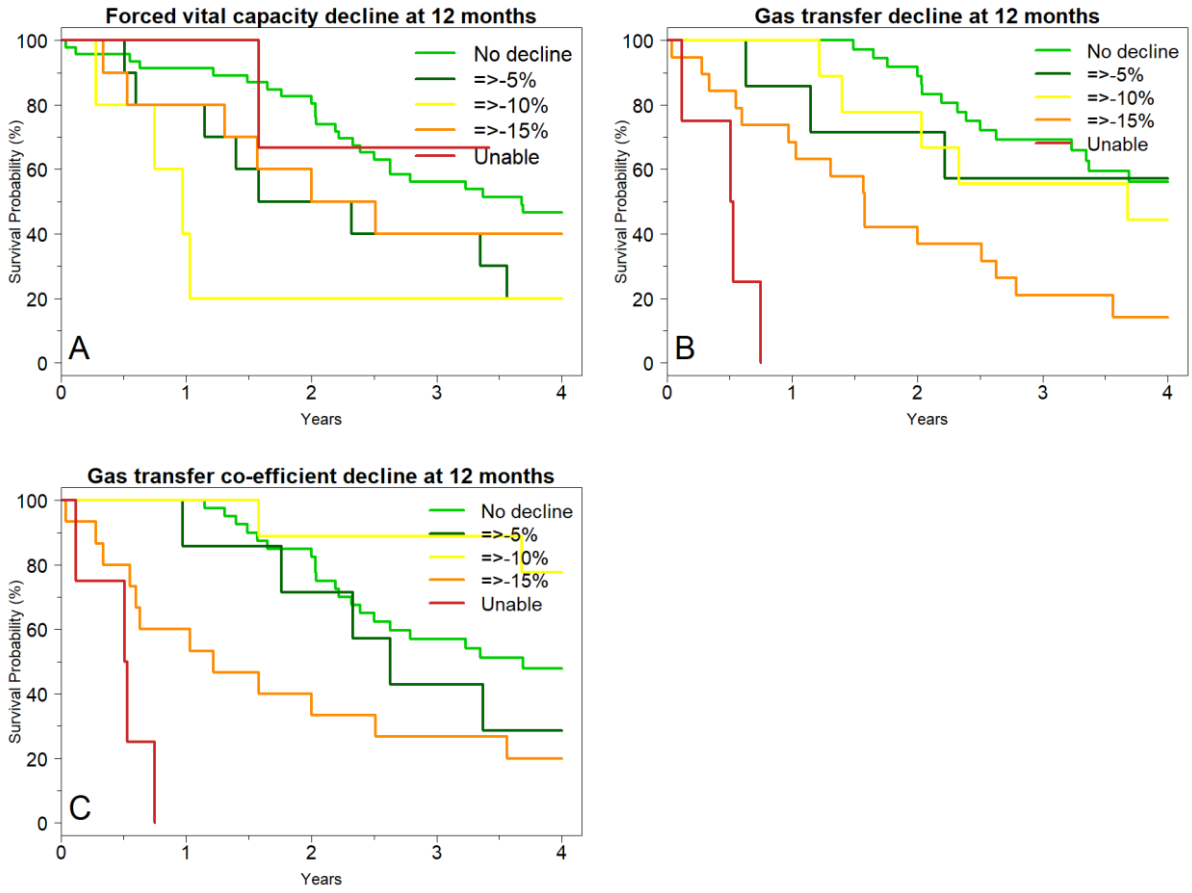


Figure 8.8. Kaplan-Meier survival estimates for decline in pulmonary function test twelve months post right heart catheterisation.

Panel A - decline in FVC, Panel B - decline in gas transfer, Panel C - decline in gas-transfer co-efficient

8.3.6.2 Multivariable assessment of outcome using longitudinal PFT changes at twelve months post RHC

Multivariable adjustment included ILD diagnosis, gender, age, ILD score at CT, baseline PFT. A 5% decline in FVC (or the inability to complete the test) remained an independent predictor of mortality or lung transplant, HR:2.36 (CI:1.19-4.66, p=0.01) (Table 8.14). A 10% decline in FVC (or the inability to complete the test) did not remain an independent predictor after multivariable adjustment. A 15% decline in TLco (or the inability to complete the test) remained an independent predictor after multivariable adjustment, HR:3.22 (CI:1.37-7.58, p=0.007), as did Kco, HR:3.60 (CI:1.48-8.71, p=0.005).

	HR (95% CI)	Adjusted HR (95% CI) ≠
12 months decline in FVC of ≥5%	2.04 (1.11-3.73)	2.36 (1.19-4.66)
12 months decline in FVC of ≥10%	1.93 (0.99-3.77)	2.04 (0.94-4.42)
12 months decline in TLco of ≥15%	4.17 (2.26-7.67)	3.22 (1.37-7.58)
12 months decline in Kco of ≥15%	3.88 (2.07-7.25)	3.60 (1.48-8.71)

Table 8.14. Univariable and multivariable Cox analysis for PFT decline twelve months post RHC.

Abbreviations: As per table 8.10. ≠ Adjusted for; ILD diagnosis, gender, age, ILD score at CT, baseline PFT of interest, and the follow up PFT. The above multivariable analysis consists of three different models. For example, in the case FVC the model included; ILD diagnosis, gender, age, ILD score at CT, baseline FVC and 6 months decline in FVC.

8.3.7 Inter-correlation of decline in FVC and gas transfer compared between ILD groups

Patients with an ILD diagnosis of IIP / CHP and were more likely to experience a deterioration in their pulmonary function tests at both; six months odds ratio (OR):5.49 (CI:2.13-14.9, p=0.004) and 12 months OR:5.55 (CI:2.02-16.7, p=0.005) compared with patients with sarcoid / CTD-ILD and idiopathic NSIP (Figure 8.9). Both remained independent after adjustment for age, gender and ILD score at HRCT (table 8.15).

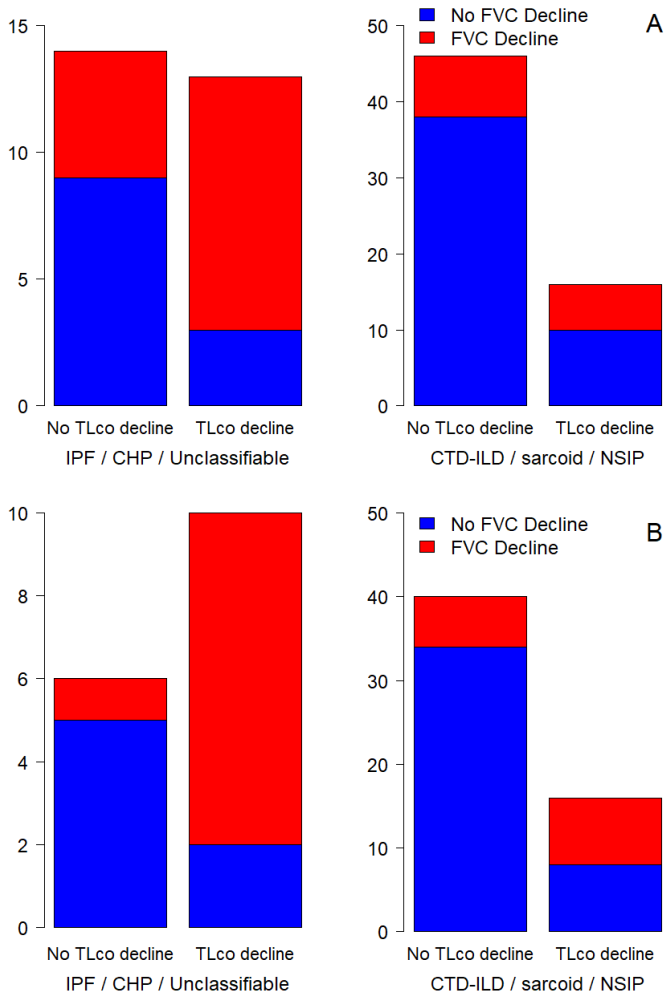


Figure 8.9. Bar plots demonstrating decline in both FVC (5%) and decline in TLco (15%) at 6 months (panel A), and 12 months (panel B).

Abbreviations as per table 8.3

	OR (95% CI)	P value	Adjusted OR (95% CI) ≠	P value
6 months decline in FVC of ≥5%	2.67 (1.21-5.95)	0.04	3.10 (1.31-5.52)	0.03
12 months decline in FVC of ≥5%	4.17 (1.59-11.5)	0.01	5.68 (1.89-18.7)	0.01
6 months decline in TLco of ≥15%	4.29 (1.93-9.79)	0.003	2.70 (1.02-7.20)	0.003
12 months decline in TLco of ≥15%	9.26 (3.37-27.2)	<0.001	12.0 (3.40-48.9)	0.01
6 months decline in both TLco and FVC	5.49 (2.13-14.9)	0.004	3.73 (1.26-11.4)	0.03
12 months decline in both TLco and FVC	5.55 (2.02-16.7)	0.005	6.64 (2.02-23.4)	0.01

Table 8.15. Logistic regression analysis evaluating decline in PFT by in patients with IIP / CHP versus CTD-ILD sarcoid.

Abbreviations: OR - odds ratio, FVC - Forced vital capacity, TLco - gas transfer, ≠ Adjusted for age, gender and ILD severity at CT

8.3.8 Longitudinal change in BNP levels at six months post RHC.

8.3.8.1 Baseline characteristics of the cohort with BNP available at six months

121 patients had a follow up BNP performed at six months. Most of the cohort consisted of patients with CTD-ILD (n=39, 32%), IPF (n=31, n=26%) and sarcoidosis (n=29, n=24%) (Table 8.16).

ILD diagnosis	Number
Connective tissue disease (CTD- ILD)	39
Idiopathic pulmonary fibrosis (IPF)	31
Sarcoidosis	29
Chronic hypersensitivity pneumonitis (CHP)	6
Non-specific interstitial pneumonitis (NSIP)	13
Unclassifiable	3
Total	121

Table 8.16. ILD Diagnoses of the patients with available follow BNP at six months

The average age of the cohort with available follow up BNP at twelve months was 62±11 (Table 8.17), and 47% were male. The mean PAP was 38±10mmHg, and mean PVR was 7.4±4.0 Wood units. The mean extent of fibrosis at CT was 45±13%.

ILD-PH Longitudinal cohort	Number of patients (n=121)
Age at right heart catheter	62±11
Gender (%, men)	47
Long term oxygen therapy prescription (%)	77
Haemodynamics *(at baseline)*	
Mean pulmonary artery pressure (mmHg)	38±10
Cardiac output (L/m)	4.1±1.2
Pulmonary capillary wedge pressure (mmHg)	10±4
Pulmonary vascular resistance (Wood units)	7.4±4.0
CT evaluation *(at baseline)*	
Extent of fibrosis (%)	45±13
Pulmonary Function Tests *(at baseline)*	
Forced Expiratory $Volume_1$ (% predicted)	58±17
Forced Vital capacity (% predicted)	60±19
Gas transfer (% predicted)	25±10
Gas transfer co-efficient (% predicted)	51±15
Brain natriuretic peptide	
BNP (ng/L)	120[51-410]

Table 8.17. Baseline demographics of the patients with available follow up BNP at six months.

8.3.8.2 BNP levels at six months and rate of change in BNP

BNP levels were evaluated in quartiles based on their distribution in the cohort. The lowest quartile of BNP (0-57ng/L) was associated with a better outcome than the other quartiles of BNP (Table 8.18, figure 8.10, panel A). There was no significant difference in outcome between the second, third and fourth quartile in terms of BNP level at six months. Investigating Quartiles of the rate of change in BNP, demonstrated that when BNP was increasing it was associated with an adverse outcome. When the rate of change in BNP was >10 ng/L per month (the equivalent of the BNP increasing from 30ng/L to 90ng/L over 6

months) it was associated with an adverse outcome, HR:2.12 (CI:1.19-3.78, p=0.01). Interestingly the second quartile of rate of change in BNP (-8 to 0.3 ng/L per month), appeared to be associated with a slightly improved risk when compared to those whose BNP fell the most, suggesting that if BNP was grossly elevated at presentation it was associated with a worse prognosis (figure 8.10, panel B). BNP levels were considered increased when they were >40ng/L (twice the upper limit of normal). When BNP was >40ng/L it was associated with an adverse outcome, HR:2.09 (CI:1.10-3.93, p=0.02) (figure 8.10, panel C). A rate of change in BNP ≥2.0 ng/L per month was associated with an adverse outcome, HR:2.39 (CI:1.56-3.65, p<0.001) (figure 8.10, panel D).

	Brain natriuretic peptide levels at six months			
	BNP (ng/L) at six months (Quartiles)			
	0-57	**58-134**	**135-296**	**≥297**
Frequency Number (%)	32 (26)	29 (24)	29 (24)	31 (26)
Cox analysis HR (CI)	Reference	2.02 (1.07-3.81)	1.85 (0.97-3.50)	2.55 (1.38-4.69)
	Rate of change in BNP at six months (Quartiles)			
	-200 to -9	**-8 to 0.3**	**0.4 to 10**	**>10**
Frequency Number (%)	30 (25)	30 (25)	30 (25)	31 (25)
Cox analysis HR (CI)	Reference	0.76 (0.40-1.44)	1.36 (0.74-2.49)	2.12 (1.19-3.78)

Table 8.18. Frequency of decline in BNP at six months post RHC, and hazard ratios using univariable Cox analysis.

Abbreviations - HR Hazard Ratio, CI - Confidence Interval.

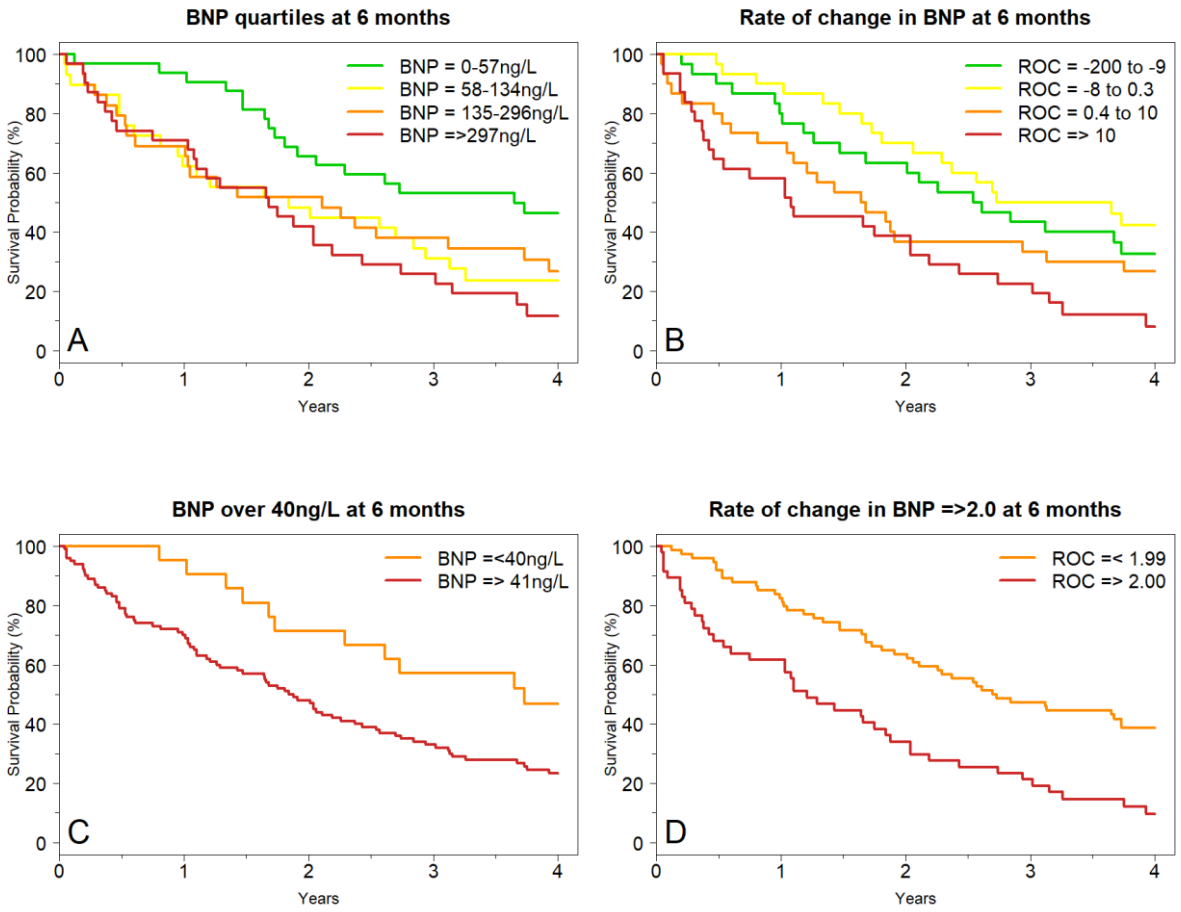


Figure 8.10. Kaplan-Meier survival estimates for BNP levels six months post right heart catheterisation.

Panel A- BNP quartiles, panel B - the rate of change in BNP in quartiles, panel C - BNP greater than 40ng/L, panel C - rate of change in BNP ≥ 2.0ng/L per month

8.3.8.3 Multivariable assessment of outcome using BNP level and changes at six months post RHC

A BNP level of >40ng/L did not remain an independent predictor following multivariable adjustment (including ILD diagnosis, gender, age, ILD score at CT, and baseline BNP levels), HR:1.94 (CI:0.96-3.90, p=0.07) (Table 8.19). A rate of change in BNP ≥2.0 ng/L per month remained an independent predictor of outcome, HR:2.63 (CI:1.62-4.25, p<0.001) following multivariable adjustment.

	HR (95% CI)	Adjusted HR (95% CI) ≠
BNP >40ng/L at six months	2.09 (1.11-3.93)	1.94 (0.96-3.90)
BNP rate of change ≥2.0 at six months	2.39 (1.56-3.65)	2.63 (1.63-4.25)

Table 8.19. Univariable and multivariable Cox analysis for BNP levels and rate of change in BNP at six months post RHC.

Abbreviations: HR - Hazard Ratio, CI - Confidence Interval. ≠ Adjusted for; ILD diagnosis, gender, age, ILD score at CT, baseline BNP.

8.3.9 Baseline characteristics of the cohort with BNP available at twelve months

96 patients had repeat BNP available for analysis twelve months post RHC. The ILD diagnoses for this group are shown in table 8.20. Patients with CTD-ILD (n=36, 38%), IPF (n=14, 15%) and sarcoid (n=30, 32%) comprised most of the group.

ILD diagnosis	Number
Connective tissue disease	36
Idiopathic pulmonary fibrosis	14
Sarcoidosis	30
Chronic hypersensitivity pneumonitis	6
Non-specific interstitial pneumonitis	10
Unclassifiable	0
Total	96

Table 8.20. ILD Diagnoses of the patients with available follow BNP at twelve months

The average age of the cohort with available follow up PFT at twelve months was 59±11 (Table 8.23), and 44% were male. The mean PAP was 38±9mmHg, and mean PVR was 7.4±3.8 Wood units. The mean extent of fibrosis at CT was 43±13% (Table 8.21).

ILD-PH Longitudinal cohort	Number of patients (n=96)
Age at right heart catheter	59±11
Gender (%, men)	44
Long term oxygen therapy prescription (%)	77
Haemodynamics (at baseline)	
Mean pulmonary artery pressure (mmHg)	38±9
Cardiac output (L/m)	4.2±1.3
Pulmonary capillary wedge pressure (mmHg)	10±4
Pulmonary vascular resistance (Wood units)	7.4±3.8
CT evaluation (at baseline)	
Extent of fibrosis (%)	43±13
Pulmonary Function Tests (at baseline)	
Forced Expiratory $Volume_1$ (% predicted)	56±16
Forced Vital capacity (% predicted)	62±19
Gas transfer (% predicted)	27±11
Gas transfer co-efficient (% predicted)	53±16
Brain natriuretic peptide	
BNP (ng/L)	128 [60-367]

Table 8.21. Baseline demographics of the patients with available follow up BNP at twelve months.

8.3.9.1 BNP levels at twelve months and rate of change in BNP

At twelve months of follow up, there was no significant difference between any of the BNP quartiles in terms of outcome (Table 8.22, figure 8.11, panel A). Quartiles of the rate of change in BNP, showed that when BNP was increasing it was associated with an adverse outcome. When the rate of change in BNP was >10 ng/L per month (the equivalent of the BNP increasing from 100ng/L to 220ng/L over 12 months) then it was associated with an adverse outcome, HR:2.67 (CI:1.09-6.54, p=0.03) (figure 8.11, panel B). When BNP levels were considered increased when they were >40ng/L (twice the upper limit of normal), it

was not associated with an adverse outcome, HR:1.55 (CI:0.73-3.29, p=0.3) (figure 8.11, panel C). A rate of change in BNP ≥1.0 ng/L per month was associated with an adverse outcome, HR:2.10 (CI:1.22-3.61, p=0.007) (figure 8.11, panel D).

	Brain natriuretic peptide levels at twelve months			
	BNP (ng/L) at six months (normal <20ng/L) (Quartiles of the cohort)			
	0-57	**58-134**	**135-296**	**≥297**
Frequency Number (%)	28 (29)	27 (28)	19 (20)	22 (23)
Cox analysis HR (CI)	Reference	0.89 (0.42-1.87)	0.95 (0.41-2.20)	1.77 (0.86-3.64)
	Rate of change in BNP at six months (Quartiles)			
	-200 to -9	-8 to 0.3	0.4 to 10	>10
Frequency Number (%)	20 (21)	34 (35)	25 (26)	17 (18)
Cox analysis HR (CI)	Reference	1.35 (0.58-3.13)	1.79 (0.77-4.20)	2.67 (1.09-6.54)

Table 8.22. Frequency of decline in BNP at twelve months post RHC, and hazard ratios using univariable Cox analysis.

Abbreviations: As per table 8.18

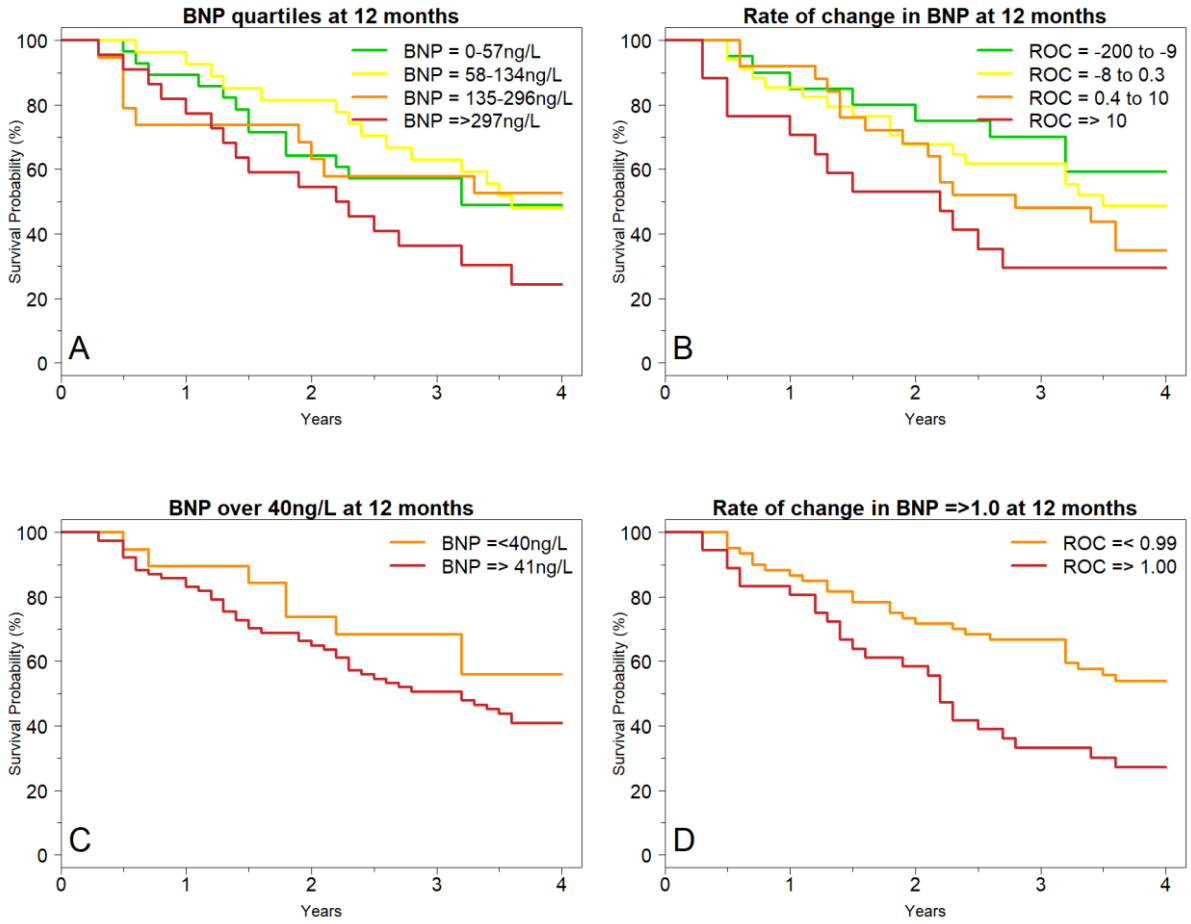


Figure 8.11. Kaplan-Meier survival estimates for BNP levels twelve months post right heart catheterisation.

Panel A - BNP quartiles, panel B - the rate of change in BNP in quartiles, panel C - BNP greater than 40ng/L, panel D - rate of change in BNP ≥1.0ng/L per month

8.3.9.2 Multivariable assessment of outcome using BNP level and changes at twelve months post RHC

A BNP level of >40ng/L was not an independent predictor following multivariable adjustment (including ILD diagnosis, gender, age, ILD score at CT, and baseline BNP levels) HR:1.01 (CI:0.42-2.48, p=0.06) (Table 8.23). A rate of change in BNP ≥1.0 ng/L per month just failed to remain an independent predictor of outcome HR:1.87 (CI:0.99-3.55, p=0.06) following multivariable adjustment.

	HR (95% CI)	Adjusted HR (95% CI) ≠
BNP >40ng/L at twelve months	1.55 (0.73-3.29)	1.01 (0.42-2.47)
BNP rate of change ≥1.0 at twelve months	2.10 (1.22-3.61)	1.87 (0.99-3.55)

Table 8.23. Univariable and multivariable Cox analysis for BNP levels and rate of change in BNP at six months post RHC.

Abbreviations: As per table 8.19. ≠ Adjusted for; ILD diagnosis, gender, age, ILD score at CT, baseline BNP.

8.3.10 Integration of longitudinal decline in pulmonary function tests with the ILD-PH prognostic score at six months

Longitudinal change in gas-transfer was integrated into the ILD-PH prognostic score at six months. Demographics of the cohort at six months was as the same as in section 8.3.5. Age and gender did not independently predict mortality in the 89 patients with repeat pulmonary function tests at 6 months (Table 8.24).

	Hazard ratio	Confidence Interval	P value
Age ≥65	1.11	0.62-1.98	0.7
Gender	0.81	0.42-1.56	0.5
IPF / CHP / Unclassifiable	2.24	1.22-4.11	0.009
TLco 20-30% predicted	2.98	0.86-10.3	0.08
TLco <20% predicted or unable to perform	6.43	1.77-23.3	0.005
Unable to perform TLco	26.2	6.78-101	<0.001
15% Relative decline TLco	2.63	1.15-6.00	0.02

Table 8.24. Multivariable Cox analysis for longitudinal change in gas transfer at six months post RHC, integrated with the ILD-PH score.

Abbreviations as per table 8.1

When age and gender were removed from the multivariable model all components of the longitudinal ILD-PH prognostic score remained independent predictors except having a gas

transfer of 20-30% predicted; HR: 3.05 (CI:0.89-10.5, p=0.08) (table 8.25). A fall in gas transfer of ≥15% remained an independent predictor, HR:2.43 (CI:1.18-5.01, p=0.02).

	Hazard ratio	Confidence Interval	P value
IPF / CHP / Unclassifiable	2.31	1.30-4.11	0.004
TLco 20-30% predicted	3.05	0.89-10.5	0.08
TLco <20% predicted	6.25	1.73-22.5	0.005
Unable to perform TLco	24.1	6.48-89.7	<0.001
15% Relative decline TLco	2.43	1.18-5.01	0.02

Table 8.25. Multivariable Cox analysis for longitudinal change in gas transfer at six months post RHC, integrated with significant components of the ILD-PH score.

Abbreviations as per table 8.1

However, as the intermediate threshold of the gas transfer (20-30% predicted) did not remain an independent predictor, the threshold was changed to ≤25% and the 20-30% threshold removed from the score. The multivariable model including the new gas transfer threshold of ≤25% is shown in table 8.27. All variables within the new longitudinal ILD-PH score remained independent predictors. The longitudinal ILD-PH Score is shown in table 8.25. The minimum value achievable was 0, and the maximum value achievable was 4. Kaplan-Meier plots showing estimated survival using the longitudinal ILD-PH prognostic score is shown in figure 8.12.

	Hazard ratio	Confidence Interval	P value
IPF / CHP / Unclassifiable	2.20	1.26-3.85	0.005
TLco <25% predicted	2.37	1.08-5.18	0.03
Unable to perform TLco	36.1	12.1-107	<0.001
15% Relative decline TLco	3.52	1.81-6.84	<0.001

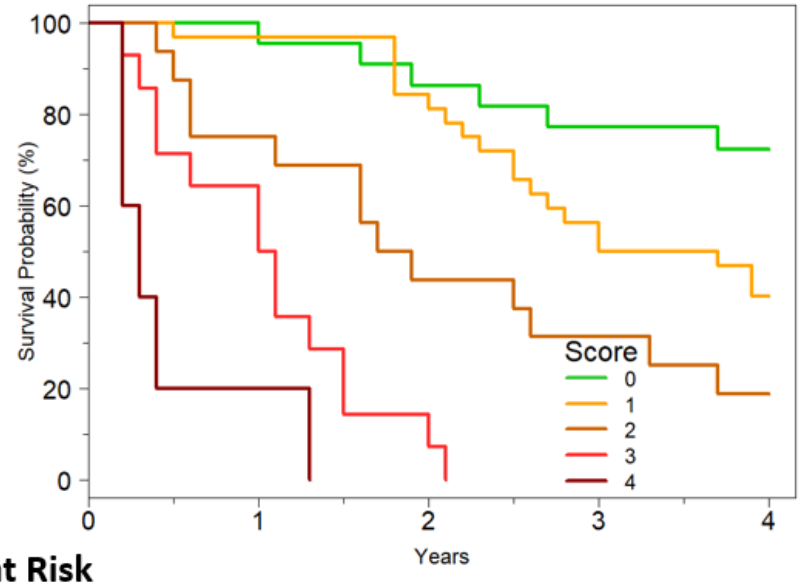
Table 8.26. Multivariable Cox analysis for longitudinal change in gas transfer at six months post RHC, integrated with the ILD-PH score and gas transfer threshold altered to less than 25%.

Abbreviations as per table 8.1

Variable		Points
ILD Subtype	Sarcoidosis	0
	CTD-ILD	0
	Idiopathic NSIP	0
	IPF	1
	Chronic HP	1
	Unclassifiable	1
TLco (% predicted)	>25.0	0
	≤25.0	1
Relative TLco decline (%)	<15%	0
	≥15%	1
Unable to perform gas transfer		3

Table 8.27. Longitudinal ILD-PH prognostic score and Index

Abbreviations as per table 8.1



Number at Risk

Score 0	**22**	**22**	**19**	**16**	**14**
Score 1	**32**	**31**	**27**	**18**	**12**
Score 2	**16**	**12**	**7**	**5**	**3**
Score 3	**14**	**9**	**2**	**0**	**0**
Score 4	**5**	**1**	**0**	**0**	**0**

Figure 8.12. Kaplan-Meir survival estimates using the Longitudinal ILD-PH prognostic score at six months, and number at risk table.

(minimum score 0, maximum score 4)

The longitudinal ILD-PH score performs well at attributing risk of death or lung transplant over the four year follow up, C-index = 0.770. 22(24.7%) were stratified in ILD-PH score 0 (low risk), 32(35.9%) in ILD-PH score 1 (moderate risk), 16(17.9%) ILD-PH score 2 (moderate-high risk), 14(15.7%) were ILD-PH score 3 (high risk), and 5(5.6%) were very high risk. The hazard ratios for the longitudinal ILD-PH score are shown in table 8.28. All scores of >0 were associated with an adverse outcome.

	Hazard ratio	**Confidence interval**	**p value**
Longitudinal ILD-PH score 0	Ref	Ref	Ref
Longitudinal ILD-PH score 1	2.50	1.00-6.27	0.05
Longitudinal ILD-PH score 2	5.60	2.12-14.8	<0.001
Longitudinal ILD-PH score 3	25.1	8.74-72.2	<0.001
Longitudinal ILD-PH Index 4	76.2	19.9-292	<0.001

Table 8.28. Longitudinal ILD-PH score Cox analysis.

8.3.11 Integration of longitudinal decline in pulmonary function tests with the ILD-PH prognostic score at twelve months

Longitudinal change in gas-transfer was integrated into the ILD-PH prognostic score at twelve months. Again, gender did not independently predict mortality in the 75 patients with repeat pulmonary function tests at 6 months (Table 8.29). The intermediate TLco threshold of 20-30% again did not predict outcome.

	Hazard ratio	Confidence Interval	P value
Age ≥65	1.91	0.92-3.95	0.08
Gender	1.31	0.63-2.72	0.5
IPF / CHP / Unclassifiable	3.19	1.39-7.33	0.006
TLco 20-30% predicted	2.02	0.55-7.46	0.3
TLco <20% predicted or unable to perform	5.31	1.41-20.0	0.01
Unable to perform TLco	27.5	4.12-183	<0.001
15% Relative decline TLco	2.13	0.98-4.62	0.05

Table 8.29. Multivariable Cox analysis for longitudinal change in gas transfer at twelve months post RHC, integrated with the ILD-PH score.

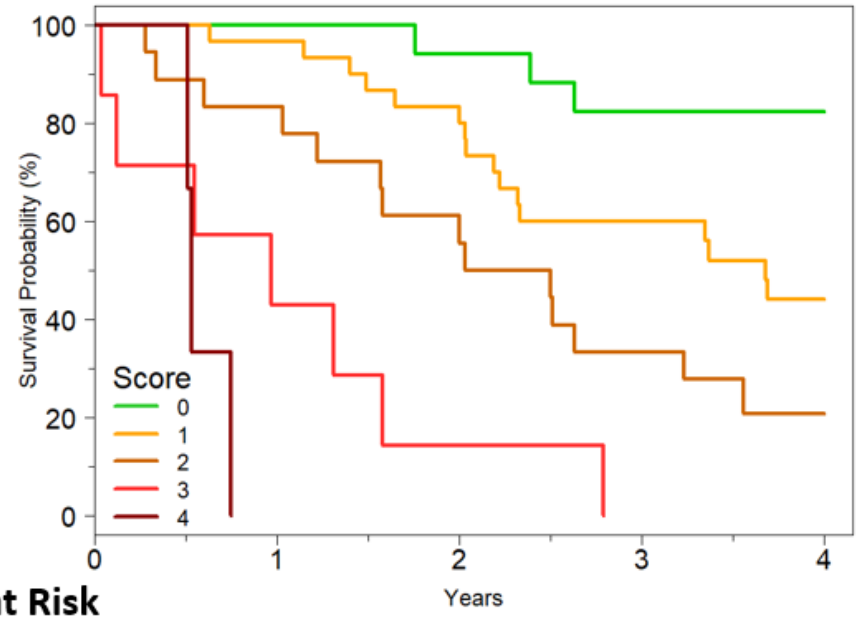
Abbreviations as per table 8.1

As occurred at six months the threshold was changed to ≤25%. When the gas transfer threshold was modified to consist of only one threshold and gender removed all factors remained independent predictors (table 8.30). A 15% decline in gas transfer was independently associated with mortality, HR: 2.94 (CI:1.46-5.94, p=0.003). The same score was applied at 12 months as is shown in figure 8.23. The Kaplan-Meier for the longitudinal ILD-PH score at 12 months is shown in figure 8.13.

	Hazard ratio	Confidence Interval	P value
IPF / CHP / Unclassifiable	2.73	1.26-5.90	0.01
TLco <25% predicted	2.61	1.07-6.36	0.03
Unable to perform TLco	37.4	7.60-184	<0.001
15% Relative decline TLco	2.94	1.46-5.94	0.003

Table 8.30. Multivariable Cox analysis for longitudinal change in gas transfer at twelve months post RHC, integrated with the ILD-PH score and gas transfer threshold altered to less than 25%.

Abbreviations as per table 8.1



Number at Risk

Score 0	**17**	**17**	**16**	**14**	**14**
Score 1	**30**	**29**	**25**	**16**	**8**
Score 2	**18**	**15**	**11**	**6**	**3**
Score 3	**7**	**3**	**1**	**0**	**0**
Score 4	**3**	**0**	**0**	**0**	**0**

Figure 8.13. Kaplan-Meir survival estimates using the Longitudinal ILD-PH prognostic score at twelve months, and number at risk table.

(minimum score 0, maximum score 4)

The longitudinal ILD-PH score performed well at attributing risk at 12 months with a C-index of 0.746. 22(27.8%) were stratified in ILD-PH score 0 (low risk), 32(40.5%) in ILD-PH score 1 (moderate risk), 16(20.2%) were ILD-PH score 2 (moderate-high risk), 14(17.7%) were ILD-PH score 3 (high risk), and 5(6.3%) were very high risk. The hazard ratios for the longitudinal ILD-PH score are shown in table 8.28. All scores of >0 were associated with an adverse outcome. The hazard ratios at 12 months are very similar to those seen at six months (table 8.31).

	Hazard ratio	Confidence interval	p value
Longitudinal ILD-PH score 0	Ref	Ref	Ref
Longitudinal ILD-PH score 1	4.00	1.16-13.8	0.03
Longitudinal ILD-PH score 2	8.01	2.29-28.1	<0.001
Longitudinal ILD-PH score 3	27.4	6.84-110	<0.001
Longitudinal ILD-PH Index 4	89.4	14.9-538	<0.001

Table 8.31. Longitudinal ILD-PH score Cox analysis.

8.4 Discussion

This longitudinal analysis has shown that the ILD-PH prognostic Index (as shown in chapter 7) continues to be a good predictor of outcome when recalculated at 6 and 12 months. The C-index for the ILD-PH Index was 0.726 at six months and 0.737 at 12 months. Interestingly gender did not remain an independent predictor of outcome at longitudinal follow up. This suggests that male gender is a risk factor for early mortality although gender is highly dependent upon ILD diagnosis. Many of the men with IPF were likely to have died (or been too unwell for repeat PFT), leaving more patients with CTD / NSIP in the cohort who have a much better prognosis. The gas transfer thresholds also failed to predict mortality at six and

twelve months. Having a severely reduced gas transfer (<20% predicted) remained an independent predictor at both six and twelve months follow up, however having a gas transfer of 20-30% did not remain an independent predictor at six or twelve months follow up. This is likely due to the small number of patients who had preserved gas transfers for comparison, just 17/89 (19%) patients at six months, and 17/75 (23%) at 12 months were in the preserved gas transfer group.

My analysis on longitudinal PFT showed that both longitudinal change in FVC and gas transfer / gas transfer co-efficient remain independent predictors of mortality after multivariable adjustment. In patients with IPF, decline in FVC is regarded as the best longitudinal measure to define disease progression (du Bois et al., 2011b, Richeldi et al., 2012), and even marginal declines of 5-10% are associated with worse outcome (Zappala et al., 2010). In our cohort ≥5% decline in FVC was common, occurring in 26/89(29%) patients at six months. A relative change of ≥5% remained an independent predictor of mortality after adjusting for age, gender, ILD-diagnosis and ILD score at CT, and baseline FVC. Reviewing the Kaplan Meier plots (figure 8.7) clearly demonstrates that in our cohort, a decline in FVC of 5% at six months carried a very similar prognostic significance as patients whose FVC declined by 15% or more. Longitudinal change in FVC is utilised in existing mortality prediction tools. In the Du Bois model, a decline in FVC of ≥10% at 6 months is the strongest predictor of mortality (du Bois et al., 2011b). Smaller changes in FVC (-5 to -9.9%) at six months also carried significance within the score; a decline of 5% was associated with a more than twofold increase in the risk of death over the next twelve months. Our findings extend those of previous studies (du Bois et al., 2011b, du Bois et al., 2011a, Zappala et al.,

2010) where even small deteriorations (5 - 9.9%) in FVC are significant. This data shows that in patients with ILD-PH any decline in FVC of more than 5% is a poor prognostic marker. At twelve months a ≥5% decline in FVC was again common, occurring in 25/77(33%) of patients. It again remained an independent predictor of mortality following multivariable adjustment. However, a 10% decline in FVC did not remain an independent predictor of mortality. This discrepancy is likely to be due to differences in the ILD diagnoses, which make up the follow up groups at 6 and 12 months. At 6 months 21/89 (24%), of patients had IPF, whereas at 12 months just 10/77 (13%) of the remaining cohort had IPF. The reduced number of patients with IPF at 12 months resulted in fewer patients with the most progressive sub-type of ILD remaining in the analysis (due to prior death).

Longitudinal trends in TLco and Kco at six months shows that 5% decline in TLco and Kco are common, occurring in 27/89 (30%), and 35/89(39%) respectively. However, neither a 5% nor 10% decline in TLco nor Kco were associated with mortality at six months. Gas transfer in general is affected by many more factors than spirometry and is therefore liable to much greater variation. A study showed that in a healthy cohort of 699 participants who performed repeated TLco measurements using a highly standardised technique, variability was 5.64% (Drummond et al., 2008). In the same study a separate group of 948 patients performed repeated measurements using routine clinical testing, where variability increased to 9.52%. Therefore in this “healthy” population if a decline of 10% was considered as significant, 15.5% to 35.5% would have been considered to have deteriorated (Drummond et al., 2008). In my analysis, patients who had deteriorated by 15% in TLco or Kco were significantly more likely to have an adverse outcome. Having a decline of 15% TLco

was common, occurring in 19/89 (21%), and 14/89 (16%) using Kco. Both remained independent following multivariable adjustment. My findings replicate prior studies, here longitudinal deterioration in TLco of 15% at six months was found to be an adverse predictor of outcome in patients with Idiopathic NSIP and IPF; however more marginal declines in TLco were not associated with mortality(Zappala et al., 2010). In scleroderma associated ILD, twelve months decline in TLco of 15% or more was an adverse predictor in patients with extensive lung fibrosis, although not in patients with milder lung fibrosis (Goh et al., 2017).

What is very clear from my data is the inability to perform either spirometry or gas transfer is common in patients with ILD-PH and is an adverse predictor of outcome. At six months 10/89 (11%) could not perform gas transfer due to inability to meet the criteria to complete the test. This was a very adverse predictor of outcome, with the inability to complete the TLco manoeuvre strongly associated with mortality, HR:7.58 (CI:2.58-8.96, $p<0.001$). This was replicated at twelve months although failure to perform the gas transfer manoeuvre was less common with just 4 (77%), it was still a very adverse predictor of outcome, HR:29.5 (CI:7.63-114, $p<0.001$). Few studies have evaluated the impact of an inability to complete either spirometry or gas transfer on prognosis. Although the inability to perform gas transfer is recognised in the original Gap model in IPF (Ley et al., 2012), ILD-Gap model (Ryerson et al., 2014) as well as the integrated baseline and longitudinal GAP model (Ley et al., 2015). It is highly likely that the inability to perform spirometry and gas transfer manoeuvres are more common in patients with ILD-PH, due to more severe hypoxaemia, and inability to breath hold.

Analysis of BNP trends at six months was extremely interesting. Although BNP is widely discussed in PAH risk assessment literature (Boucly et al., 2017b, Al-Naamani et al., 2016) there are limited studies evaluating longitudinal BNP analysis and risk stratification. Longitudinal BNP trends have been evaluated in 1426 patients as part of the Reveal registry (Frantz et al., 2018). They demonstrated that prognosis was worst when BNP was elevated at baseline (340 pg/ml), and when it remained over this level at twelve months. Patients with preserved BNP at diagnosis, which remained low at follow-up had the best prognosis. My findings at six months are similar. It appeared that having an elevated BNP >40ng/L, was associated with a worse prognosis, HR:2.09 (CI:1.11-3.93, p=0.02). Although, this did not remain an independent predictor following multivariable adjustment, and this trend had not been seen in the original baseline cohort and was not repeated in the analysis at twelve months. As the rate of change in BNP increased, prognosis was adversely affected; a rate of change >10 ng/l per month was a poor prognostic marker, HR:2.12 (CI:1.19-3.78, p=0.01). A rate of change in BNP of >2.0ng/L per month over six months, remained an independent predictor of mortality, following multivariable adjustment. However, although a rate of change in BNP of >1.0ng/L per month at twelve months predicted outcome in a univariable setting, it did not remain an independent predictor following multivariable adjustment. Analysis of the quartiles of rate of change of BNP showed that patients who had the largest fall in BNP did not necessarily have the best prognosis. It would seem logical that patients whose BNP fell the furthest following treatment, would have a better prognosis than patients with smaller reductions in BNP. Although if RV function is severely impaired at presentation (and BNP very elevated) then treatment with vasodilators / ILD optimisation

may cause BNP to fall, with some improvement in RV function. However, as RV function was severely impaired at presentation then the improvement may not be sustained as deterioration in ILD or pulmonary vascular disease is likely to result in greater deterioration compared to patients who had preserved RV function at baseline (and lower BNP). Therefore, longer-term outcome appears to be worse when features of RV impairment are present at the initial diagnosis. My previous analysis using CTPA shows that RV dilatation is common in ILD-PH and was present even when pulmonary pressure did not meet the diagnostic criteria for PH and was independently associated with a worse outcome. Therefore, RV functional assessment appears to be extremely important in ILD-PH.

I attempted to integrate both longitudinal trends in FVC and gas transfer into the longitudinal ILD-PH score although analysis showed that future trends in pulmonary function tests were strongly linked to ILD diagnosis. Patients with IPF / CHP and unclassifiable ILDs were more likely to show a decline in FVC, OR:4.17 (CI:1.59-11.5, p=0.01), and TLco, OR:9.26 (CI:3.37-27.2, p<0.001) at twelve months. Furthermore, patients with IIP / CHP were much more likely to experience a decline in both FVC and TLco at six, OR:5.49 (CI:2.13-14.9, p=0.004), and twelve months, OR:5.55 (CI:2.02-16.7, p=0.005). Therefore, integration of longitudinal FVC and TLco was not possible as FVC did not remain an independent predictor of outcome at multivariable analysis and was strongly linked to ILD diagnosis and TLco decline.

Neither age nor gender remained independent predictors at six or twelve months in the longitudinal ILD-PH score. I have already discussed earlier that male gender is associated with an adverse short-term outcome. At RHC in the baseline cohort, the median age was

62±11, and 51% were men. By six months the average age was 61±11 years and 47% were men. At twelve months the average age had fallen to 59±12, and just 39% were men. It is likely this very high attrition of older men over the course of the study led to age and gender no longer predicting outcome.

The finding that only severely reduced gas transfer (<25%) predicated mortality at longitudinal assessment is due to the advanced nature of both the degree of ILD affecting the patients in the cohort as well as the advanced nature of their PH. The patients in the ILD-PH cohort appear to have a worse severity of ILD (when judged by FVC); patients in the original GAP validation cohort had an FVC of 68±18% (Ley et al., 2012), in the ILD GAP model patients with IPF, FVC was 69±18 (Ryerson et al., 2014). Whereas in the ILD-PH cohort at baseline the FVC was 60±19%, at six months it was 61±16%, and at twelve months was 62±17%. Gas transfer was even more severely reduced comparing the cohorts, reflecting additional pulmonary vascular disease. The original GAP validation cohort had a TLco of 46±14% (Ley et al., 2012) (Ryerson et al., 2014). However, In the ILD-PH cohort TLco was much more severely reduced at baseline where the TLco was 24±9 %, nearly half when compared to the original GAP validation cohort. The ILD-PH cohort appear to have a more severe ILD extent (using FVC) when compared to these large well described cohorts in which mortality prediction tools have been developed and validated.

A decline in TLco of 15% remained an independent predictor in the multivariable model. The univariable hazard ratio for experiencing a 15% reduction in TLco was HR:4.81 (CI:2.58-8.96, p<0.001), and adjusted hazard ratio was HR:3.52 (CI:1.81-6.84, p<0.001), at six months. This is very similar to the hazard ratio found in 1777 IPF patients with follow up TLco at six

months, where a 15% decline was associated with an adverse outcome, HR:4.61 (CI:2.53-8.38, p<0.001) (du Bois et al., 2011b). At six months the C-statistic for the recalculated ILD-PH index was 0.726, whereas using the longitudinal ILD-PH score the C-statistic increased to 0.770 (a difference of 0.044). At 12 months the C-statistic for the recalculated ILD-PH index was 0.737, whereas using the longitudinal ILD-PH score the C-statistic increased to 0.746 (a difference of 0.009). These are very similar increase in the C-index as occurred when additional longitudinal predictors were added to the GAP index (Ley et al., 2015). When change in FVC at 24 weeks was integrated into the GAP model with the presence/absence of a respiratory hospitalisation the C-index increases from 0.757 to 0.785 (a difference of 0.028).

8.5 Limitations

The dominant limitation of this analysis is the retrospective nature of the study in addition to the small number of patients with available data at 6 and 12 months for follow up. Unfortunately, the low number of patients with available data reflects the horrendous nature of a diagnosis of ILD-PH leading to such a high attrition rate. The longitudinal ILD-PH score would need further study in a larger external cohort with refinement and external validation prior to any clinical use. It was not possible to integrate longitudinal trends in BNP with longitudinal trends in PFT as too few patients had both tests performed in the same follow up period. Unfortunately, insufficient patients had follow-up echocardiograms. All patients in the ILD-PH cohort were investigated for PH due to a clinical suspicion of PH, and most had advanced ILD as well as PH. Therefore, they are likely to be at the severe end of the spectrum in terms of disease severity; the prognostic implication discussed in chapter 7

and this chapter only apply to patients with similar demographics and disease severity. It is likely that if ILD-PH is found as part of screening then the prognostic implications of declines in PFT are likely to be less severe.

8.6 Conclusion

- ILD diagnosis is the strongest determinant of prognosis being associated with increased risk of future decline in PFT, and death and or need for lung transplantation.
- Male gender and older age are risk factors for short-term mortality.
- A BNP which is increasing by >2.0ng/L per month (equivalent of an increase in BNP of 12ng/L) at six months is associated with an adverse outcome.
- A decline in FVC of just 5-10% at six months is an adverse predictor in ILD-PH.
- A decline in TLco of ≥15% is a very adverse predictor of outcome in ILD-PH.
- A strength of the study is that many of the findings (decline in FVC of 5-10%, and decline in TLco of ≥15%) mirror those found in ILD, although the mortality risks are higher in ILD-PH.

CHAPTER 9 OVERALL DISCUSSION AND FUTURE DIRECTIONS

The findings of my research confirmed that it is possible to predict PH occurring in patients with ILD, with reasonable sensitivity and specificity. Furthermore, longitudinal changes in non-invasive markers predict mortality in ILD-PH patients. I demonstrated in chapter four that the integration of multiple non-invasive markers is better at predicting PH than each individual non-investigation in isolation. The approach I used was to utilise non-invasive investigations which are routinely available and already commonly employed to risk stratify for PH occurring in ILD. The integration of CT, echocardiographic and PFT variables results in an easily applicable score to use in a patient with suspected ILD-PH. False negatives do occur, therefore, if clinical suspicion of PH is high and the implication of PH essential then diagnostic RHC is still recommended. False positives are common, and my research has shown that patients with ILD develop significant signs of PH without meeting the diagnostic criteria for PH at RHC studies. This is a novel finding which deserves further research, particularly as I demonstrated in chapter six that RV dilatation at CTPA was an adverse predictor of outcome regardless of PH status. Although the mechanism and evaluation of why patients with ILD develop PH / RV dysfunction is beyond the subject matter of this thesis I have developed theories which require further evaluation. Patients with CTD-ILD and sarcoid can develop PH independent of the underlying ILD therefore likely have different mechanisms of PH compared to patients with IIP. Therefore, to discuss my potential theory on the development of PH I will utilise patients with IIP. There is a very large body of

evidence (my thesis included), which shows that PH severity is not linked to ILD severity when assessed by CT or PFT. Most patients with IIP do not seem to develop PH, and those that do develop PH do so once the ILD is relatively advanced. The development of PH is likely influenced by the following;

- Age
- Rate of ILD progression
- The occurrence of a period of rapid worsening in ILD / exacerbation
- Severity of hypoxia
- Genetic predisposition to develop PH – (which could help explain the variable penetrance of PH)
- Other associated conditions (OSA / sleep disordered breathing / Hypertension)

A proposed timeline discussing the development of PH in relation to ILD severity is shown in figure 9.1.

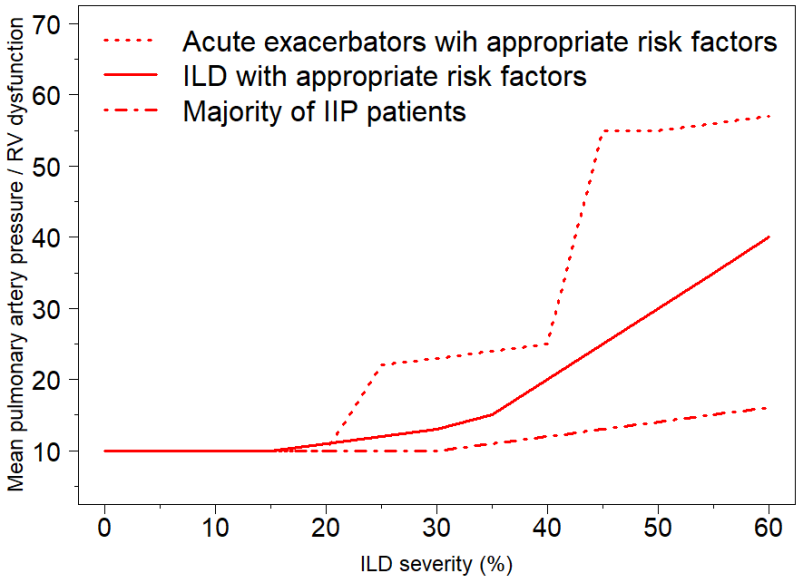


Table 9.1 Proposed timeline for patients with IIP developing PH related to ILD severity

Abbreviations: ILD - Interstitial lung disease, IIP - Idiopathic interstitial pneumonias

It is likely that the threshold of ILD severity which causes PH / RV dysfunction is highly variable from patient to patient with IIP. This could explain why ILD severity does not correlate with invasive pressures at RHC. The pulmonary vasculature can absorb large deteriorations in ILD severity without the development of PH / RV dysfunction in the majority of IIP patients through pulmonary vascular remodelling. However, once the threshold of ILD severity is reached (and pulmonary vascular function is affected) then minor increases in ILD severity could result in large increases in pulmonary pressure / RV dysfunction. As illustrated in figure 9.1, patients who have exacerbations and have the appropriate risk factors are likely to experience rapid increase in pulmonary pressure / develop RV dysfunction in response to those exacerbations, in a stepwise manner. IIP patients who develop PH are likely sensitized (through genetics) to create an aberrant

pulmonary vascular remodelling response (or RV dysfunction) in response to ILD. The threshold at which this occurs is different from patient to patient. However, most patients with IIP do not develop PH, but do seem to show increase in pulmonary pressure / RV dysfunction as the disease progresses but do not develop overt signs of PH. It is also possible that once the pulmonary vascular remodelling process / RV dysfunction has been triggered then a progressive increase in pressure / RV dysfunction occurs independently of ILD severity.

In IIP I suggest we should move away from focusing on invasive pulmonary pressure and move to assess RV function and signs of PH non-invasively. Patients with RV dilatation were at an increased risk of death / lung transplant compared to patients with preserved RV:LV ratio at CT. RV dilatation occurred without PH being demonstrated at RHC and negatively affected outcome. A move to commence PH therapies (in a clinical trial) based on non-invasive signs of PH would make it dramatically easier (and cheaper) to evaluate pulmonary vasodilators in IIP associated PH. It is also likely that early and goal orientated therapy with vasodilators may result in an improved prognosis rather than focusing on patients who have developed severe PH. It seems illogical to wait until PH is severe to trial vasodilators, as RV function will already be adversely affected. I suspect the earlier pulmonary vasodilators are started the greater the impact they can have on negating the progressive increase in pulmonary pressure / RV dysfunction.

My thesis has also demonstrated that the development of PH is a very negative prognostic factor when it occurs in patients with ILD. The demonstration that mortality prediction tools such as the ILD-GAP index are not valid in patients with ILD-PH confounds their use in

patients with ILD-PH and supports detailed evaluation for PH. This highlights the importance in the careful assessment for PH especially where an increased risk of mortality will have profound impact on management such as lung transplant consideration. Mortality rates were approximately double in patients with ILD associated PH compared to those predicted by using the ILD-GAP index.

It is interesting that I did not find invasive haemodynamics to be independent predictors of mortality. It is highly probable that the nature of the cohort is a significant reason for this. There were insufficient numbers of patients without PH at RHC for a direct comparison of PH versus no PH. Furthermore, it seems that patients who develop signs of PH when assessed non-invasively but do not have PH at RHC are at an increased risk of mortality and therefore are not a fair direct comparison. Patients who had PH demonstrated at RHC likely had more aggressive management of contributing co-morbidities, than patients who did not have PH at RHC. Treatment with vasodilators may also play a role in lessening the impact of elevated PVR and mPAP. A positive impact was seen in patients treated with vasodilators although treatment with vasodilators was strongly linked to ILD subtype, and patients who died soon after RHC were much less likely to be treated with vasodilators.

The best predictor of prognosis was the underlying ILD subtype, with patients with IIP and chronic HP having the worst prognosis. However, the type of ILD will have strongly influenced the decision to perform RHC initially. In addition, patients with IIP are likely to have undergone RHC at a later stage as there is a lack of useful interventions in this group, leading to significant lead-time bias. Although the finding of PH in any patient with an IIP should lead to immediate consideration and referral for lung transplant if appropriate.

Functional tests such as TLco and Kco performed best in predicting mortality in ILD-PH. This is because they account for both the ILD and PH disease component.

My development of a mortality prediction tool, which can be used in patients with confirmed ILD-PH is a step towards the individualisation of mortality prediction in patients with confirmed ILD-PH. The baseline and longitudinal mortality prediction tool will require validation in an external cohort before it can be utilised clinically. The main utility of the mortality prediction tool could be to reassure that in patients with a low score that continued optimisation is appropriate, with regular re-assessment using the longitudinal model. It could also be used to screen patients to recruit to clinical trials evaluating vasodilators in patients with IIP-PH. Patients in the highest risk group are very unlikely to derive any significant benefit from vasodilators and should be optimised and referred for lung transplant evaluation and or palliative care. Unfortunately, it was not possible to integrate echocardiographic longitudinal markers of pulmonary vascular disease due to a lack of follow up echocardiograms. However, BNP has shown that it is valid in predicting outcome. An increase in BNP was associated with mortality and lung transplant at 6 and 12 months. Patients whose BNP increased (evaluated by the rate of change in BNP) had a worse prognosis compared to patients whose BNP remained stable or improved. The fact that BNP fell in some patients suggests that optimisation of associated co-morbidities and vasodilators may have a role in improving prognosis in ILD-PH. It also shows that PH in ILD is important and drives mortality rather than mortality just being dictated by the interstitial disease component.

In terms of future directions, I would like to consider the following:

- Evaluate CTPA derived RV:LV ratio in IIP patients at initial diagnosis.
- Validate the PH prediction scores to predict PH in an external cohort.
- Validate the baseline and longitudinal PH prognostic models in an external cohort.
- To help understand why patients develop PH / RV dysfunction I would very much like to consider the following. A longitudinal observational study evaluating patients with IIP to include assessment of pulmonary vascular and ILD status at baseline and longitudinally at six monthly intervals to include the following:
    - PFT
    - BNP
    - Echocardiogram
    - Six-minute walk test.
    - CT pulmonary angiogram (at baseline only and repeated if clinically indicated)
    - Cardiac MR (baseline and then annually)
    - History of acute exacerbations / respiratory hospitalisations
    - Genetic evaluation (at baseline only)

I would like to finally conclude that I have shown that the development of PH occurring in patients with ILD is an extremely adverse predictor of outcome. It is possible to predict which patients with ILD have PH using non-invasive evaluation although if absolute certainty is required then RHC is necessary. In addition, I showed that mortality prediction can be improved by evaluation of novel CTPA derived RV:LV ratio, and baseline demographics and PFT variables. Furthermore, that knowledge of PH status is essential for accurate risk stratification. Finally, I showed that longitudinal trends in PFT and BNP predict mortality and need for lung transplant in patients with ILD-PH.

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