Pulmonary hypertension: clinical phenotypes and non-invasive risk stratification

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PULMONARY HYPERTENSION RESEARCH

List of contents

Acknowledgements 3

Summary (300 words) 4

Table of Contents 5

List of Tables 9

List of Figures 10

Abbreviations 12

Declaration 17

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Summary (300 words)

Pulmonary arterial hypertension (PAH) is a rare disease and often heterogeneous at clinical presentation. There has been significant interest in the use of clinical parameters to assess risk, and two risk stratification tools exist. I aimed to assess whether additional non-invasive investigations could improve upon current approaches. In addition, I sought to evaluate specific phenotypes in pulmonary hypertension, including patients with idiopathic PAH (IPAH) who have mild lung disease. Data were obtained from clinical databases at a large PAH referral centre.

When assessing clinical phenotypes, I identified that the presence of minor lung disease in patients with IPAH was a strongly negative prognostic marker, and these patients did not demonstrate an improvement in exercise capacity in response to PAH targeted therapy.

For risk stratification I aimed to identify thresholds for low (<5%), intermediate (5-10%) and high (>10%) risk of one-year mortality, as in other widely-used approaches. Risk could be stratified using three non-invasive assessments: cardiac MRI, incremental shuttle walking test (ISWT) and emPHasis-10 quality of life score. In contrast to current risk stratification approaches, thresholds for cardiac MRI were able to identify a large proportion of patients (63%) at low-risk of one-year mortality. In addition, cardiac MRI was able to add discriminative value to currently used risk stratification scores. EmPHasis-10 was an independent predictor of mortality, and in a risk stratification approach was able to identify patients with distinct levels of one-year mortality. For the ISWT, a 10% improvement in exercise capacity was an independent prognostic marker of survival, and thresholds derived at baseline accurately stratified risk at follow-up.

This thesis demonstrates that non-invasive assessments can be used either in isolation or in conjunction with other prognostic parameters in patients with PAH. The thresholds proposed could be considered for incorporation into widely-used risk stratification scores.

Table of Contents

1. Introduction 20

1.1 An overview of pulmonary hypertension 20

1.1.1 The Pulmonary Circulation and Pulmonary Hypertension 20

1.1.2 Definition 20

1.1.3 Epidemiology and Classification 21

1.1.4 Pathophysiology of PAH 23

1.1.5 Genetic Mutations 24

1.1.6 Clinical Presentation 24

1.1.7 Arrhythmias 25

1.1.8 Treatments 25

1.1.8.1 Supportive treatment 26

1.1.8.1.1 Anticoagulation 26

1.1.8.2 Transplantation 27

1.1.8.3 PAH-specific therapies 27

1.1.8.3.1 Calcium channel blockers 27

1.1.8.3.2 Nitric oxide pathway 28

1.1.8.3.3 Endothelin pathway 28

1.1.8.3.4 Prostacyclin pathway 29

1.1.8.4 Choice of treatment 29

1.2 Risk Stratification 29

1.2.1 Risk Stratification in Medicine 29

1.2.2 Introduction to Risk Stratification in PAH 30

1.2.3 Initial risk stratification studies in PAH 30

1.2.4 Non-modifiable risk 31

1.2.5 Survival between different forms of PAH 32

1.2.6 Lung disease in the context of IPAH 32

1.2.7 Exercise assessment in PAH 33
1.2.8 Right Ventricular Function as a Marker of Prognosis 34
1.2.9 Blood biomarkers 34
1.2.10 Recent developments in risk score calculators 35
1.2.11 REVEAL 2.0 risk score calculator 37
1.2.12 ESC/ERS Risk Stratification 40
1.2.12.1 Validation of the ESC/ERS Risk Stratification Tool 41
1.2.13 The Role of Imaging in Risk Stratification 44
1.3 Conclusion and Hypothesis 47
1.4 Format of thesis 47
2. Methods 49
2.1 Introduction 49
2.1.1 Follow up 50
2.1.2 Investigations and assessments 50
2.1.2.1 Database interrogation and data integration 50
2.1.2.1 Statistical analysis 50
2.1.2.1.1 Specific statistical methods in chapter 4 51
2.1.2.2 Quality of life scores 52
2.1.2.3 Pulmonary function testing 52
2.1.2.4 Incremental Shuttle Walking Test 52
2.1.2.5 Computed tomography (CT) scans 52
2.1.2.1 Right heart catheterisation 53
2.1.2.2 Cardiac MRI and image acquisition 53
2.1.2.3 Ethical approval 54
3. Partial anomalous pulmonary venous drainage in patients presenting with suspected pulmonary hypertension: a series of 90 patients from the ASPIRE registry 55
3.1 Abstract 56
3.2 Introduction 57

3.3 Methods 57
3.4 Results 58
3.5 Discussion 66
3.6 Conclusions 69
4. Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension 70
4.1 Abstract 71
4.2 Introduction 72
4.3 Methods 72
4.4 Results 74
4.5 Discussion 91
4.6 Conclusion 93
5. Identification of cardiac MRI thresholds for risk stratification in pulmonary arterial hypertension 94
5.1 Abstract 96
5.2 Introduction 97
5.3 Methods 98
5.4 Results 101
5.5 Discussion 119
5.6 Conclusion 121
6. Maximal exercise testing and risk stratification in pulmonary arterial hypertension 122
6.1 Abstract 124
6.2 Introduction 125
6.3 Methods 126
6.4 Results 127
6.5 Discussion 141
6.6 Conclusion 143

7. EmPHasis-10 health-related quality of life score predicts outcomes in patients with idiopathic and connective tissue disease-associated pulmonary arterial hypertension: results from a UK multi-centre study 144
7.1 Abstract 145
7.2 Introduction 146
7.3 Methods 147
7.4 Results 148
7.5 Discussion 158
7.6 Conclusion 160
8. Summary and Conclusion 161
8.1 Limitations 163
8.2 Future directions 163
8.3 Conclusion 164
9. Bibliography 165

List of Tables

Table 1: Classification of Pulmonary Hypertension 23
Table 2: Risk stratification model from ESC/ERS guidelines 41
Table 3: Baseline Demographics 59
Table 4: Comparison of patients with isolated PAPVD and PAPVD + ASD* 65
Table 5: Baseline demographics and maximal treatment data 79
Table 6: Univariate and Multivariate Cox regression analysis of prognostic factors in patients with $IPAH_{no\text{-}LD}$ or $IPAH_{mild\text{-}LD}$ 80
Table 7: Baseline demographics in patients with subtypes of $IPAH_{mild\text{-}LD}$ compared with $IPAH_{no\text{-}LD}$ 81
Table 8: Demographics for subgroups of IPAH 87
Table 9: Demographics in patients with follow-up data available 88
Table 10. Baseline and follow-up incremental shuttle walking test distance and emPHasis-10 score 90
Table 11: Baseline demographics in patients undergoing cardiac MRI 103
Table 12: Cardiac MRI metrics 104
Table 13: Univariate and multivariate analysis on whole cohort (scaled) 105
Table 14: Univariate analysis in Discovery Cohort 107
Table 15: Percentage mortality at 4, 6 and 12 months by quintile group 108
Table 16: Percentage mortality at 4, 6 and 12 months 112
Table 17: Levels of the ISWT and mortality per level for patients with IPAH and PAH-CTD 129
Table 18: Baseline demographics in all forms of pulmonary hypertension 130
Table 19: Baseline demographics in patients with IPAH and PAH-CTD 131
Table 20: Association between ISWT level and haemodynamic and cardiac MRI parameters 133
Table 21**:** Patient characteristics 149
Table 22: Correlation of emPHasis-10 and WHO functional class with walk distance and pulmonary haemodynamics 150
Table 23: Univariate and multivariate analysis in incident patients 154

List of Figures

Figure 1: Summary diagram showing multiple mechanisms of pulmonary hypertension 22
Figure 2: The three major pathways targeted by current treatments in pulmonary arterial hypertension. 28
Figure 3: Kaplan-Meier plot demonstrating survival between different forms of PAH and PH 32
Figure 4: The REVEAL Risk Calculator 36
Figure 5: The REVEAL 2.0 updated risk score calculator 39
Figure 6: Layout of the incremental shuttle walking test 52
Figure 7: Contouring of cardiac border at MRI during diastole 54
Figure 8: Scatter plot demonstrating haemodynamic parameters for patients with PAPVD 60
Figure 9: Flow chart demonstrating frequency of SV-ASD and haemodynamic parameters in patients with PAPVD. 62
Figure 10: Contrast-enhanced CT scans of variants of PAPVD 67
Figure 11: Flow chart demonstrating selection of patients for participation in study 76
Figure 12: Survival from diagnosis in $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$ 77
Figure 13: Survival by subtype of lung disease in $IPAH_{mild\text{-}LD}$ 78
Figure 14: Change at first follow-up beyond 90 days in a) ISWD; b) emPHasis-10 83
Figure 15: Survival in IPAH patients with no lung disease ($IPAH_{no\text{-}LD}$) stratified by DLCO <45% predicted ($IPAH_{DLCO<45}$) versus DLCO ≥45% predicted ($IPAH_{DLCO\geq45}$) 84
Figure 16: Distribution of DLCO %predicted in patients with $IPAH_{no\text{-}LD}$ 85
Figure 17: Survival in patients with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$ treated with oral combination therapy within 6 months of diagnosis 86
Figure 18: Flow chart demonstrating patients included and reasons for exclusion 102
Figure 19: Histograms displaying quintile groups and percentage mortality at one year for cardiac MRI variables (discovery) 111
Figure 20: Histograms displaying percentage mortality at one year for derived thresholds for cardiac MRI variables (test cohort) 113
Figure 21: Kaplan Meier survival curves based on cardiac MRI thresholds 115
Figure 22: Impact of adding cardiac MRI to widely used risk stratification approaches 116
Figure 23: ROC curves showing potential added value of cardiac MRI in conjunction with risk stratification approaches 117
Figure 24: LOESS regression curve demonstrating predicted mortality at one-year for cardiac MRI parameters 118
Figure 25: Kaplan Meier survival curves for a) ISWD in all PH; b) ISWD in IPAH and PAH-CTD 132

Figure 26: Kaplan Meier survival curves for ISWT 134
Figure 27: A scatterplot showing individual baseline and follow-up ISWT distances, and mortality or transplant within one-year of follow-up ISWDin patients aged <50 135
Figure 28: A scatterplot showing individual baseline and follow-up ISWT distances, and mortality or transplant within one-year of follow-up ISWD 138
Figure 29: Kaplan Meier analysis demonstrating survival in risk stratification approaches..... 139
Figure 30: Risk of mortality by REVEAL 2.0 score, using variations of REVEAL 2.0 incorporating ISWD 140
Figure 31: Distribution of emPHasis-10 score by WHO functional class at baseline 151
Figure 32: Kaplan Meier survival curves demonstrating survival from baseline emPHasis-10 score. 155
Figure 33: Survival in incident patients with WHO functional class III symptoms, dichotomised by emPHasis-10 score ≤33 or ≥34..... 156
Figure 34: Change in walk distance (ISWD or 6MWD) in patients whose emPHasis-10 score deteriorated by ≥9 or improved by ≥9 between baseline and follow-up..... 157

Abbreviations

6MWD	6-Minute Walking Distance
6MWT	6-Minute Walking Test
ACHD	Adult Congenital Heart Disease
ANP	Atrial Natriuretic Peptide
ASD	Atrial Septal Defect
ASPIRE	Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre [registry]
APVD	Anomalous Pulmonary Venous Drainage
APAH	Associated Pulmonary Arterial Hypertension
BMI	Body Mass Index
BMPR2	Bone morphogenic protein receptor type II
BNP	B-type Natriuretic Peptide
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CCB	Calcium Channel Blocker
CHD	Congenital Heart Disease
CI	Cardiac Index
CLD-PH	Pulmonary Hypertension due to Chronic Lung Disease
CMR	Cardiac Magnetic Resonance
CNP	C-type Natriuretic Peptide
CO	Cardiac Output
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension [registry]
COPD	Chronic Obstructive Pulmonary Disease

CPET	Cardio-Pulmonary Exercise Test
CT	Computed Tomography
CTD	Connective Tissue Disease
CTEPH	Chronic Thrombo-Embolic Pulmonary Hypertension
CTPA	Computed Tomography Pulmonary Angiogram
D_{LCO}	Diffusing Capacity of the lung for Carbon Monoxide
EIF2AK4	Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4
ECG	Electrocardiogram
ERS	European Respiratory Society
ESC	European Society of Cardiology
ET	Endothelin
FPHR	French Pulmonary Hypertension Registry
HIV	Human Immunodeficiency Virus
HPAH	Heritable Pulmonary Arterial Hypertension
HRCT	High Resolution Computed Tomography
IPAH	Idiopathic Pulmonary Arterial Hypertension
ILD	Interstitial Lung Disease
ISWD	Incremental Shuttle Walking Test Distance
ISWD %pred	Incremental Shuttle Walking Test Distance, displayed as %predicted for age, sex and body mass index
ISWT	Incremental Shuttle Walking Test
LA	Left Atrium
LD	Lung disease
LHD	Left Heart Disease
LOESS	Locally weighted Estimated Scatterplot Smoothing

LVEDV	Left Ventricular End-Diastolic Volume
LVEDVi	Left Ventricular End-Diastolic Volume indexed (indexed for body surface area)
LVEDVi %pred	Left Ventricular End-Diastolic Volume index, displayed as percent predicted for age and sex
LVEF	Left Ventricular Ejection Fraction
LVEF %pred	Left Ventricular Ejection Fraction, displayed as percent predicted for age and sex
LVESV	Left Ventricular End-Systolic Volume
LVESVi	Left Ventricular End-Systolic Volume index (indexed for body surface area)
LVESVi %pred	Left Ventricular End-Systolic Volume index, displayed as percent predicted for age and sex
mPAP	mean Pulmonary Arterial Pressure
MDC	Minimal Detectable Change
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
MvO_2	Mixed Venous Oxygen Saturation
NIH	National Institute of Health
NO	Nitric Oxide
NT-proBNP	N-terminal pro b-type natriuretic peptide
OPG	Osteoprotegerin
OSA	Obstructive Sleep Apnoea
PA	Pulmonary Artery
PAH	Pulmonary Arterial Hypertension
PAH-CHD	Pulmonary Arterial Hypertension in association with Congenital Heart Disease
PAH-CTD	Pulmonary Arterial Hypertension in association with Connective Tissue Disease
PAH-SYMPACT	Pulmonary Arterial Hypertension-Symptoms and Impact

PAPVD	Partial Anomalous Pulmonary Venous Drainage
PAWP	Pulmonary Arterial Wedge Pressure
PDE-5	phosphodiesterase-5
PDS	Personal Demographics Service
PH	Pulmonary Hypertension
PH-LHD	Pulmonary Hypertension due to Left Heart Disease
PHSANZ	Pulmonary Hypertension Society of Australian and New Zealand [registry]
PoPH	Portopulmonary hypertension
PROM	Patient-Reported Outcome Measure
PVOD	Pulmonary Veno-Occlusive Disease
PVR	Pulmonary Vascular Resistance
RA	Right Atrium
RAC	Relative Area Change
RAP	Right Atrial Pressure
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management
RHC	Right Heart Catheterisation
ROC	Receiver Operating Characteristic
RV	Right Ventricle
RVEDV	Right Ventricular End-Diastolic Volume
RVEDVi	Right Ventricular End-Diastolic Volume index (indexed for body surface area)
RVEDVi %pred	Right Ventricular End-Diastolic Volume index, displayed as percent predicted for age and sex
RVEF	Right Ventricular Ejection Fraction
RVEF %pred	Right Ventricular Ejection Fraction, displayed as percent predicted for age and sex

RVESV	Right Ventricular End-Systolic Volume
RVESVi	Right Ventricular End-Systolic Volume index (indexed for body surface area)
RVESVi %pred	Right Ventricular End-Systolic Volume index, displayed as percent predicted for age and sex
SPAHR	Swedish Pulmonary Arterial Hypertension Registry
SPVDU	Sheffield Pulmonary Vascular Disease Unit
SV-ASD	Sinus Venosus-Atrial Septal Defect
VMI	Ventricular Mass Index
WHO	World Health Organisation
WHO-FC	World Health Organisation-Functional Class
WSPH	World Symposium on Pulmonary Hypertension
WU	Wood Units

Declaration

I, Robert Alexander Lewis, confirm that the Thesis is my own work. I am aware of the University's Guidance on the Use of Unfair Means (www.sheffield.ac.uk/ssid/unfair-means). This work has not been previously been presented for an award at this, or any other, university.

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Publications and presentations arising from this thesis

Publications

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Lewis, R. A., Thompson, A. A. R., Billings, C. G., Charalampopoulos, A., Elliot, C. A., Hamilton, N., . . . Condliffe, R. Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension. *European Respiratory Journal*. 2020;55(6).

Lewis, R. A., Billings C.G., Bolger, A., Bowater, S., Charalampopoulos, A., Clift, P., . . . Condliffe, R. Partial anomalous pulmonary venous drainage in patients presenting with suspected pulmonary hypertension: a series of 90 patients from the ASPIRE registry. *Respirology.* 2020; 25: 1066– 1072.

Lewis, R.A., Durrington, C., Condliffe, R., Kiely, D.G. BNP/NT-proBNP in pulmonary arterial hypertension: time for point of care testing? *European Respiratory Review.* 2020;29(156):200009.

Lewis, R.A., Armstrong, I., Bergbaum, C., Brewis, M.J., Cannon, J., Charalampopoulos, A., . . . Condliffe, R. EmPHasis-10 health-related quality of life score predicts outcomes in patients with idiopathic and connective tissue disease-associated pulmonary arterial hypertension: results from a UK multi-centre study. *European Respiratory Journal.* 2020 (in press).

Lewis, R.A., Billings, C.G., Hurdman, J., Smith, I.A., Austin, M., Armstrong, I.J., . . . Kiely, D.G. Maximal exercise testing and risk stratification in pulmonary arterial hypertension. *Annals of the American Thoracic Society*. 2020 (in press).

Billings, C. G., **Lewis, R.**, Hurdman, J. A., Condliffe, R., Elliot, C., Thompson, A. A. R., . . . Kiely, D. Express: The incremental shuttle walk test predicts mortality in non-group 1 pulmonary hypertension: results from the ASPIRE Registry. *Pulmonary Circulation*. 2019;9(2):2045894019848649.

Billings, C. G., **Lewis, R.**, Armstrong, I. J., Hurdman, J. A., Smith, I. A., Austin, M., . . . Kiely, D. G. Incremental Shuttle Walking Test Distance Is Reduced in Patients With Pulmonary Hypertension in World Health Organisation Functional Class I. *Frontiers in Medicine*. 2018;5:172.

Ramjug, S., Adão, R., **Lewis, R.**, Coste, F., de Man, F., Jimenez, D., . . . Vonk-Noordegraaf, A. Highlights from the ERS International Congress 2018: Assembly 13 – Pulmonary Vascular Diseases. *ERJ Open Research*, *5*(1), 00202-2018.

Middleton, J. T., Maulik, A., **Lewis, R.**, Kiely, D. G., Toshner, M., Charalampopoulos, A., . . . Rothman, A. Arrhythmic burden and outcomes in pulmonary arterial hypertension. *Frontiers in Medicine*. 2019;6:169.

Charalampopoulos, A., **Lewis, R.**, Hickey, P., Durrington, C., Elliot, C., Condliffe, R., . . . Kiely, D. G. Pathophysiology and diagnosis of pulmonary hypertension due to left heart disease. *Frontiers in Medicine*. 2018;5:174.

Presentations to learned societies

Lewis, R., Billings, C., Johns, C., Hurdman, J., Hamilton, N., Elliot, C., . . . Condliffe, R. (2018). Anomalous pulmonary venous drainage (APVD) in patients with suspected pulmonary hypertension (PH). *European Respiratory Journal*. 2018;52(suppl 62):PA3080.

Billings, C., **Lewis, R.**, Hurdman, J., Armstrong, I., Smith, I., Austin, M., . . . Kiely, D. (2018). Incremental Shuttle Walk Test predicts survival in non-Group 1 Pulmonary Hypertension without a ceiling effect. *European Respiratory Journal*. 2018;52(suppl 62):PA3322.

Billings, C., **Lewis, R.**, Armstrong, I., Hurdman, J., Smith, I., Austin, M., . . . Kiely, D. (2018). Incremental shuttle walking test distance is reduced in patients with pulmonary hypertension in WHO Functional Class I. *European Respiratory Journal*. 2018;52(suppl 62):PA3323.

Lewis, R., Billings, C., Johns, C., Hurdman, J., Hamilton, N., Elliot, C., . . . Condliffe, R. (2018). Identifying partial anomalous pulmonary venous drainage (PAPVD) in patients presenting with suspected pulmonary hypertension (PH). *Thorax.* 2018;73**:**A104.

Lewis, R., Cogliano, M., Johns, C. S., Billings, C. G., Hamilton, N., Elliot, C. A., . . . Kiely, D. G. (2019). Cardiac MRI: Identifying Thresholds to Predict Mortality in Pulmonary Arterial Hypertension. *American Thoracic Society International Conference Abstracts: American Thoracic Society.* 2019. p. A2809-A.

Lewis, R., Billings, C., Hurdman, J., Smith, I., Austin, M., Armstrong, I., . . . Kiely, D. (2019). The Incremental Shuttle Walking Test Can Be Used to Risk Stratify Patients with Pulmonary Hypertension as Per the European Respiratory/Cardiac Society Guidelines. *American Thoracic Society International Conference Abstracts: American Thoracic Society*. 2019. p. A2507-A.

1. Introduction

1.1 An overview of pulmonary hypertension

1.1.1 The Pulmonary Circulation and Pulmonary Hypertension

The pulmonary circulation has evolved to allow maximal efficiency of gas exchange at the alveolar membrane, by operating at low pressure and high flow through the pulmonary arteries and capillaries. Persistent elevation of pressure in this system is termed pulmonary hypertension (PH), and was initially classified by the World Health Organisation (WHO) in 1973 into Primary (now known as idiopathic pulmonary arterial hypertension) and Secondary, depending on whether a specific cause was found (1). Pulmonary hypertension ranges from typically mild elevations of pulmonary artery pressure seen in the context of significant cardiac and respiratory disease (2-6) to more severe elevations of pulmonary artery pressure seen in pulmonary arterial hypertension which is characterised by a small vessel vasculopathy, and chronic thromboembolic pulmonary hypertension where a small vessel vasculopathy may be seen in addition to more proximal obstruction of the pulmonary vasculature (7-9). Whereas pulmonary hypertension is not uncommon in the setting of significant cardiac and respiratory disease, forms of pulmonary hypertension for which specific therapies are licensed (specifically pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension) are relatively rare (10-12).

1.1.2 Definition

Normal pulmonary arterial pressure has previously been identified as 14.0 ±3.3 mmHg (13) and even at the first World Symposium on Pulmonary Hypertension (WSPH) it was identified that normal pulmonary arterial pressure does not exceed 20 mmHg (1). Despite this, until recently pulmonary hypertension was defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg (14, 15). During the course of this research project, at the 6th WSPH in 2018, an updated haemodynamic definition of precapillary pulmonary hypertension was proposed, consisting of a mPAP >20 mmHg with associated pulmonary vascular resistance (PVR) ≥3 Wood units. In this research project, unless otherwise stated, pulmonary hypertension refers to patients with a mPAP ≥25 mmHg. The focus of this project is primarily on patients with pulmonary arterial hypertension (PAH), which refers to patients with elevated pulmonary arterial pressure related to a vasculopathy and has traditionally been defined haemodynamically as a mPAP ≥25, with a PVR ≥3 Wood units and a pulmonary arterial wedge pressure ≤15 mmHg (16).

The term exercise pulmonary hypertension has previously been used to refer to patients who developed a mPAP >30 mmHg on exertion (17). This definition was abandoned following the 4th and 5th WSPH and current guidance advises avoidance of the term as it cannot be accurately defined (18).

1.1.3 Epidemiology and Classification

Following several world symposia, most recently the 6th WSPH in Nice (2018), pulmonary hypertension is now subcategorised into groups based on diseases that exhibit similar clinical and pathological characteristics (Table 1), although an overlap between conditions is increasingly recognised (19-21).

One of the most common causes of pulmonary arterial hypertension worldwide is thought to be schistosomiasis but this is uncommon in the developed world (22). Idiopathic PAH (IPAH) is rare and the exact incidence is unclear but is thought to be <5 cases per million per year (12). Approximately 4% of patients with PAH have a family history (termed heritable or familial PAH), with the majority of these patients having a genetic mutation, although sporadic cases with no family history may also have a genetic mutation (23-25). Patients with heritable PAH may have a similar clinical presentation to patients with IPAH, although often present at a younger age with more severe haemodynamics and are thought to have poorer outcomes (26, 27). In the past, idiopathic pulmonary arterial hypertension was considered to be a disease that exclusively affected young women and, while this is now recognised as inaccurate, females are more frequently affected than males, although males have a worse prognosis (28).

Pulmonary arterial hypertension is associated with connective tissue diseases, particularly systemic sclerosis where the prevalence is around 10%, and screening programmes are in place which may use algorithms including DETECT (29, 30). Systemic sclerosis can also cause elevation of the pulmonary arterial pressures through a number of non-vasculopathic mechanisms, including interstitial lung disease, and left ventricular diastolic dysfunction (30).

The onset of PAH has also been associated with the use of a number of drugs and toxins, including anorexigens, which led to a surge in cases in the 1960s due to aminorex, and in the 1990s due to fenfluramine (31). Benfluorex, used as a treatment for diabetes though has pharmacological similarities to fenfluramine, was also associated with PAH and was in use until 2009 (32). All of these drugs, which have now been withdrawn from the market, share molecular similarities to amphetamines, the use of which has been deemed a risk factor for PAH (33).

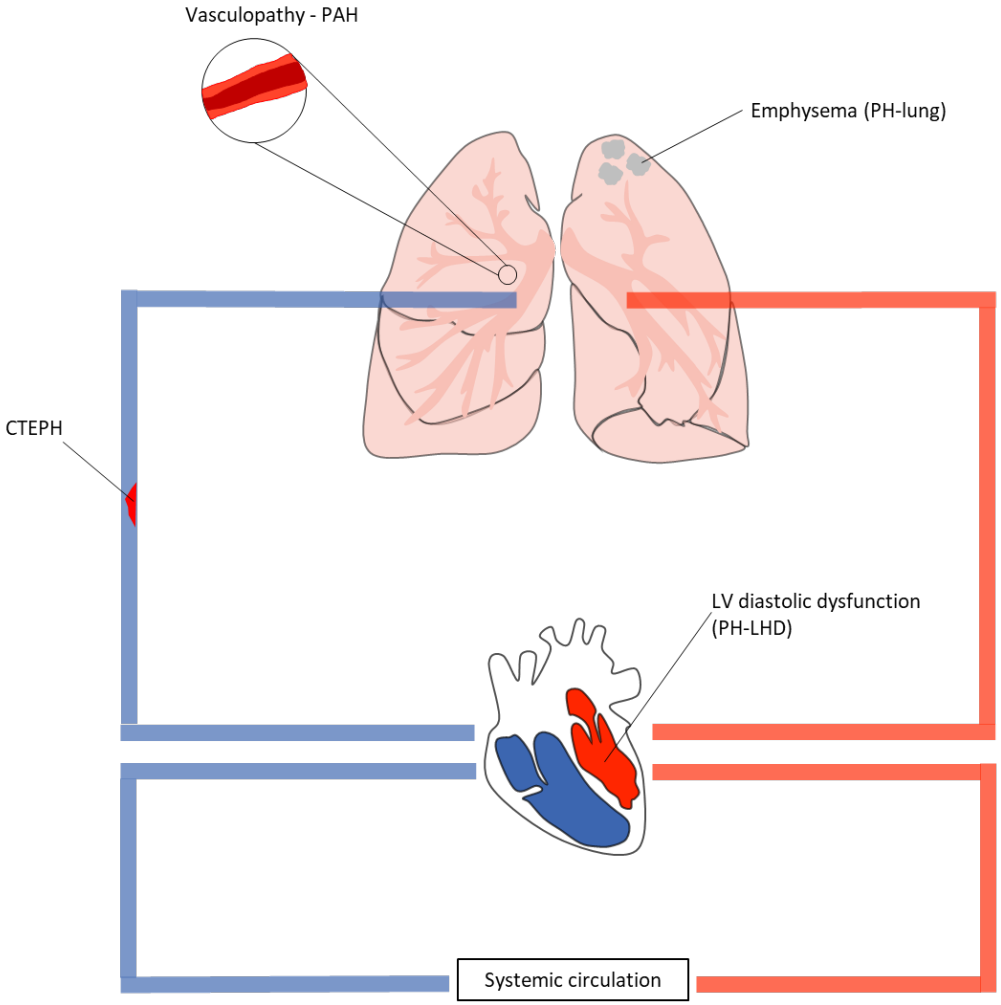

Figure 1: Summary diagram showing multiple mechanisms of pulmonary hypertension

Abbreviations: PAH = pulmonary arterial hypertension, PH = pulmonary hypertension, CTEPH = chronic thromboembolic pulmonary hypertension, LV = left ventricular, LHD = left heart disease

Table 1: Classification of Pulmonary Hypertension

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 haemangiomatosis
1''. Persistent pulmonary hypertension of the newborn (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 Haematologic 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

1.1.4 Pathophysiology of PAH

A number of mechanisms can cause increased pulmonary vascular resistance, including hypoxic vasoconstriction as seen in obstructive lung disease, and conditions that reduce luminal flow at the pulmonary vascular bed, such as pulmonary emboli (34). In PAH, however, there is typically remodelling of the small vessel pulmonary arteries. This consists of vasoconstriction, medial hypertrophy, micro-thrombosis, plexiform lesion formation, and adventitial proliferation; these pathological features are collectively termed a vasculopathy (35-37). Initially vasoconstriction was

thought to play a key role in the pathophysiology of PAH, however it is now recognised that this is a dominant feature in less than 10% of patients (38).

The vascular changes cause a rise in pulmonary vascular resistance, which leads to right ventricular strain. The usually thin-walled right ventricle hypertrophies and increases contractility without any change in stroke volume, termed “coupling”, allowing it to temporarily cope with mildly elevated pressures. As the disease progresses, the RV subsequently dilates and heart rate rises in an attempt to maintain cardiac output. This causes increased metabolic demand, and ventriculo-arterial uncoupling develops as a result. Right ventricular failure ensues and cardiac output falls, eventually leading to death (39).

1.1.5 Genetic Mutations

Bone morphogenic protein receptor type II (BMPR2) was the first causative mutation identified in PAH. It is still thought to be the most common, identified by genetic analysis in 84% of PAH patients with a family history, but only 14% of patients without. Since BMPR2 was identified in 2000, a number of other mutations have been described in PAH, as well as EIF2AK4 (Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4) which has been demonstrated as predisposing to pulmonary veno-occlusive disease (PVOD) (40).

Approximately 10-20% of patients affected by anorexigen-induced PAH carry a BMPR2 mutation (31, 41). In addition, the penetrance of BMPR2 is low at around 20-30% (42). These factors suggest that susceptibility to PAH is increased in patients with genetic mutations but that a further provoking risk factor may be required to induce vasculopathic changes.

Genetic counselling and screening are offered by some PAH centres, though due to incomplete penetrance not all patients who test positive for mutations will develop PAH (42). Some guidelines suggest screening asymptomatic patients who are found to have the mutation with yearly echocardiograms (43). As with all incurable diseases, genetic screening of affected relatives remains controversial.

1.1.6 Clinical Presentation

While patients may be asymptomatic at presentation, the majority present with significant disease, typically in WHO Functional Class III and with significant elevation of the pulmonary arterial pressures (44). Symptoms at presentation typically include dyspnoea, fatigue and exercise limitation but as the disease progresses symptoms and signs of low cardiac output develop, including pre-syncope, peripheral oedema and, in severe disease, syncope (45, 46). Palpitations may occur as a result of arrhythmias, usually supraventricular in nature and most commonly atrial flutter and atrial fibrillation

(47). Peripheral oedema and pericardial effusion signify significant right heart failure and are usually late manifestations (46). Pulmonary arterial hypertension is often thought of as a disease that affects the pulmonary circulation and right heart in isolation, however a number of systemic consequences have been identified. Whilst some of these consequences, such as liver dysfunction and renal failure, may in part be caused by reduced cardiac output and venous congestion (48), the pathophysiology of other systemic disorders such as thyroid disease, which has an prevalence of 20% in PAH, is unclear (49).

1.1.7 Arrhythmias

Patients with PAH are prone to developing supraventricular arrhythmias, and the cumulative incidence has been found to be as high as 25% over a 5 year period (50). Both atrial flutter and atrial fibrillation appear to develop with similar frequency (47, 51). The mechanism for the development of atrial fibrillation in PAH, which in the general population is caused by left atrial enlargement, is unclear. The proposed mechanism for atrial flutter is that increased right atrial pressure induces right atrial stretch and subsequent development of fibrosis, as suggested by electrophysiological studies (51).

Arrhythmias appear to develop in those with more severe haemodynamics. Patients with a higher baseline mRAP, mPAP and PVR, as well as those with a lower cardiac output, have been found to be at greatest risk when compared with those who remain in sinus rhythm (50).

Onset of arrhythmia correlates with clinical deterioration. Tongers *et al* demonstrated that 84% of patients with PAH who developed a supraventricular arrhythmia presented with clinical decompensation, and clinical condition improved in those who had restoration of sinus rhythm (52). Those refractory to cardioversion, who all had atrial fibrillation, had a mortality of 82% over an average of 11 months following onset of arrhythmia compared to patients who remained in sinus rhythm who had a mortality of 6% with an average follow-up of 26 months (52). This study is, however, limited by the relatively small number of patients with an arrhythmia (n=27). These data may suggest that sinus rhythm restoration is important in patients with supraventricular arrhythmia, although large prospective data are lacking.

1.1.8 Treatments

Over the course of approximately 20 years, there has been significant development in treatments available for patients with PAH. At the time of the 2nd WSPH only two treatments were available for patients with pulmonary arterial hypertension: patients who exhibited a vasodilator response at right

heart catheterisation were treated with high dose calcium channel blockers, and patients with severe disease were treated with continuous infusions of intravenous epoprostenol (53).

1.1.8.1 Supportive treatment

Prior to the availability of targeted treatments, management of patients with pulmonary hypertension was focused on supportive care. Alongside targeted treatments, these still form an important part of clinical management. Oxygen prescription guidance in patients with pulmonary arterial hypertension is limited. Patients are typically considered for long term oxygen therapy when PaO2 falls below 8 kPa, in keeping with studies performed on patients with other forms of lung disease (54).

No randomised controlled trials have assessed the use of diuretics in patients with PAH but they appear to provide symptomatic benefit to patients with peripheral oedema. Diuretics also reduce right atrial pressure which, when elevated, is recognised to be an important marker of adverse outcome (55, 56).

Clinicians increasingly recommend exercise rehabilitation for patients with pulmonary hypertension, a treatment which is now recognised as safe, and a recent Cochrane review of five randomised controlled trials identified improvements of 60 metres in 6-minute walking test distance in response to structured exercise training (57, 58). Studies have typically focused on specialist pulmonary hypertension rehabilitation programmes, although community-based programmes such as pulmonary and cardiac rehabilitation may also be effective (59).

1.1.8.1.1 Anticoagulation

The role of anticoagulation in patients with IPAH remains unclear. Post mortem studies have revealed that thrombotic lesions are common in patients with IPAH (60), and clotting abnormalities have also been reported (61). Despite this, results from clinical studies and registry data have been conflicting and guidance is therefore limited (62). The German Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry identified a survival benefit in patients with IPAH who were on oral anticoagulation, whereas an analysis of the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) registry did not show such a benefit (63, 64). Randomised controlled trial data are lacking, and decisions regarding commencing anticoagulation are typically determined on a case by case basis. The role of anticoagulation in other forms of PAH is even less clear, particularly in PAH-CTD where patients may have increased risk of gastro-intestinal bleeding, and routine anticoagulation is not recommended (65).

1.1.8.2 Transplantation

For patients with severe and refractory disease, lung or heart/lung transplantation may be recommended. Due to the rare nature of the disease, patients with PAH constitute a small number of those undergoing transplantation, and gastro-oesophageal dysmotility/reflux can prevent listing for transplantation in patients with PAH due to systemic sclerosis (66-68). Early referral for transplantation is recommended as it allows pre-transplant identification and optimisation of comorbidities (69). In addition, in the UK, patients may not be established on triple therapy (excluding selexipag) until they have been accepted as suitable for lung transplant (70).

1.1.8.3 PAH-specific therapies

Currently, in addition to calcium channel blockers, there are more than 10 individual pharmacological treatment options available, which target three main pathways (Figure 2).

1.1.8.3.1 Calcium channel blockers

The potential role for calcium channel blockers (CCBs) or calcium channel antagonists has been long-recognised and was first described in the 1980s (71). Pulmonary vasodilator testing identifies patients in whom the vasculopathy is particularly contributed to by reversible vasoconstriction (53), and vasoreactivity testing is performed at right heart catheterisation by administrating inhaled nitric oxide or intravenous prostanoid. The definition of a positive response to vasoreactivity testing has varied over time, but is currently defined as a drop in mPAP of ≥10mmHg, to reach an absolute value of ≤40mmHg, with no deterioration in cardiac output (18). The percentage of patients with IPAH who exhibit this positive response has differed between studies but is approximately 5-15% of patients tested, of whom approximately half display long-term response (72-74). Patients who have a positive response at vasoreactivity testing have better outcomes, even when not treated with CCBs (74).

Figure 2: The three major pathways targeted by current treatments in pulmonary arterial hypertension. Reproduced in print with permission of the rights holder; permission not granted for online repository.

1.1.8.3.2 Nitric oxide pathway

Nitric oxide (NO) is an important factor in smooth muscle relaxation, and reduced NO production and availability is a key feature of endothelial dysfunction (75, 76). The nitric oxide pathway is targeted by phosphodiesterate-5 (PDE-5) inhibitors (tadalafil and sildenafil) and cyclic guanine monophosphate stimulators (riociguat).

1.1.8.3.3 Endothelin pathway

Endothelin-1 is a potent vasoconstrictor, and targets two receptors ET_A and ET_B (76, 77). Three specific pharmacological endothelin receptor antagonists (ERAs) are currently licensed to target this pathway:

bosentan and macitentan are dual endothelin-1 receptor antagonists, whereas ambrisentan targets ET_A in isolation (78).

1.1.8.3.4 Prostacyclin pathway

Prostacyclin is a vasodilator produced by endothelial cells, and deficiency in PAH has been long-recognised (79). Prostacyclin primarily targets the IP receptor, and in addition to causing vasodilatation, appears to reverse some of the vascular remodelling seen in PAH (80-82). Prostanoids are administered parenterally, via nebuliser or continuous subcutaneous/intravenous infusion. Epoprostenol is a synthetic equivalent of prostacyclin, whereas treprostinil and iloprost are analogues (80). Selexipag is an oral selective IP receptor antagonist which has recently been approved for use in the UK.

1.1.8.4 Choice of treatment

Selection of treatment for patients with PAH may depend on disease severity, comorbidities and interaction with other medications. The value of up-front oral combination therapy (typically a PDE-5 inhibitor and ERA) in patients with PAH was recognised in 2015, and typically now constitutes the usual initial treatment strategy for the majority of patients with PAH (83). Patients with very significant disease at diagnosis, or those felt to be at high risk of early mortality, may commence immediately on prostanoid treatment (18). Funding in the UK limits individual treatment to two concurrent therapies, apart from selexipag which may be taken as a third agent, or patients who have been deemed suitable for lung or lung/heart transplantation who may take three concurrent treatments (70).

1.2 Risk Stratification

1.2.1 Risk Stratification in Medicine

The concept of risk stratification is long-standing in medicine and its use is widespread. Many examples exist, including the Framingham data widely used in the primary prevention of cardiovascular risk. The principles apply across a wide range of fields from staging in cancer to assessing severity in pneumonia.

Risk stratification is important as patients with the same disease often have varied outcomes. In a clinical setting, the use of risk stratification tools allows clinicians to use a number of parameters and variables to more accurately predict outcomes based on specific and individual features. Risk stratification tools can therefore be used to assist treatment decisions and inform advanced care planning decisions with patients.

1.2.2 Introduction to Risk Stratification in PAH

In IPAH, life expectancy prior to the advent of specific and targeted therapies was very poor with a median survival of 2.8 years (84). With the development of treatments such as epoprostenol, prognosis and outcomes have improved (85, 86). These targeted treatments primarily act as vasodilators and are aimed at reducing pulmonary vascular resistance and preventing right ventricular failure.

It is increasingly understood that patients with PAH are a heterogeneous group and that outcomes vary significantly between different phenotypes. While initial treatment may consist of oral combination therapy, patients with significant haemodynamic disease or adverse clinical signs may require more advanced therapies including nebulised or continuous intravenous treatment. These represent significant burden on patients (87). Being able to understand which patients are at highest risk of deterioration can guide treatment escalation decisions when considering parenteral treatment, and can assist with decisions regarding timing of transplantation.

When describing patients with PAH, incident refers to those that are newly diagnosed whereas prevalent describes those that already have a diagnosis. It is recognised that incident patients have a poorer outcome than prevalent patients. The French registry followed 674 patients prospectively for 3 years, and demonstrated that 3-year survival in incident patients was 51%, compared to 71% in the prevalent group (88).

1.2.3 Initial risk stratification studies in PAH

The first paper to assess risk in pulmonary hypertension was the National Institute of Health (NIH) published in 1991 (84). The registry reports on a relatively small number of patients (n = 194) recruited from multiple centres. It is noteworthy that this paper was published before pulmonary hypertension was defined beyond primary and secondary disease. In addition, diagnostic techniques in the assessment of pulmonary hypertension have evolved; for instance, the incidence of pulmonary embolus has increased three-fold between 1985 and 2009, presumably due to advances in imaging, which may potentially affect diagnostic certainty in this study (89). Finally, treatment at the time was limited to supportive management including diuretics and oxygen at a time when no PAH targeted therapy had been approved, resulting in a very poor median survival of 2.8 years. These factors affect comparisons of the NIH data with more recent studies.

The study identified parameters conferring higher risk and derived an equation consisting of three variables: mPAP, mean right atrial pressure (RAP), and cardiac index. Although they lacked a validation cohort, they identified an equation to predict patient survival at one, two and three-years:

P(t) = [H(t)]A(x,y,z)
H(t) = [0.88 - 0.14t + 0.01t^2]
A(x,y,z) = e(0.007325x + 0.0526y – 0.3275z)

Where:
P(t) indicates the patient's chances of survival and t = 1, 2, or 3 years) after diagnosis:
x = mean pulmonary artery pressure
y = mean right atrial pressure
z = cardiac index

The equation was subsequently validated in a cohort of 61 patients (90). The NIH registry was a landmark paper at the time that recognised the importance of right ventricular dysfunction, and has been utilised by a large number of clinical trials since when determining the effects of new treatments on survival.

Thenappan *et al* sought to assess whether the NIH equation remained valid, following the now-widespread use of PAH specific treatments. They demonstrated in a cohort of 576 patients that the equation underestimated life expectancy, which may be multifactorial but likely due in part to availability of PAH specific treatments (91). With heightened awareness of the disease compared to in 1991, it is also possible that patients were diagnosed earlier, facilitating prompt intervention. Thenappan *et al* proposed an updated equation but, again, they did not validate this (91).

-

1.2.4 Non-modifiable risk

Non-modifiable risk is an important consideration in PAH; although these factors cannot be improved, they still contribute to the risk profile. Increasing age, male sex and family history of PAH have all been recognised as predisposing to poorer outcomes. Benza *et al* demonstrated that patients aged over 60 had a greater risk of mortality (hazard ratio 1.9), while males aged over 60 had a hazard ratio of 2.78 (44). While male sex appears to confer a poorer prognosis, PAH registries consistently report a significantly higher prevalence of the disease in females, ranging from 58% to 79% (28, 44).

Genetic association is well-recognised in PAH; approximately 70-80% of patients with a family history of PAH are identified as having a mutation in the BMPR2 gene. Increasingly it is recognised that there are likely to be a number of other genetic mutations which contribute to the development of PAH (92). Benza *et al* were the first to identify that patients with a family history of PAH had a higher risk of early death (44). The reasons for this are uncertain; studies demonstrate that patients with BMPR2 mutation have more severe haemodynamics, although whether having the mutation directly increases the risk of death is unclear, with conflicting findings between studies (44, 93).

1.2.5 Survival between different forms of PAH

In addition to the non-modifiable risk factors outlined above, the specific cause of PAH is also important in determining prognosis. In the ASPIRE (Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre) registry, Hurdman *et al* demonstrated that while survival differed between pulmonary hypertension groups 1-4, even within group 1 survival was significantly different (94). In a large group of incident patients, those with PAH-CHD with Eisenmenger's physiology lived longer than those with IPAH, and outcomes in PAH due to systemic sclerosis were significantly worse (Figure 3). This was also seen in the large, multi-centre French registry (88) which identified a number of important factors influencing survival, including the form of PAH, and concluded that forms of Group 1 disease other than IPAH (i.e. PAH-CTD, PAH-CHD, porto-pulmonary hypertension (PoPH), PAH related to HIV infection) should be separated from IPAH for survival analysis in future studies, as this appeared to affect outcomes. Therefore, while group 1 diseases share similar pathophysiological characteristics, there are clear differences in outcomes and the need for early treatment escalation may vary between the individual causes.

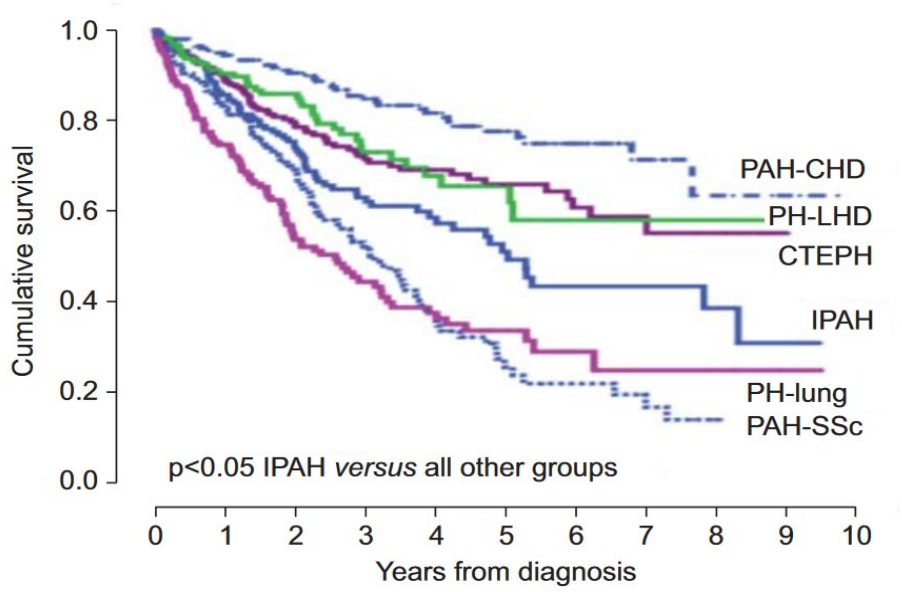

Figure 3: Kaplan-Meier plot demonstrating survival between different forms of PAH and PH, indicating best prognosis in patients with PAH-CHD and worst prognosis in PAH due to systemic sclerosis (PAH-SSc) Adapted from Hurdman et al (2012). Reproduced with permission of the ERS 2018. European Respiratory Journal 2012 39: 945-955; DOI: 10.1183/09031936.00078411

1.2.6 Lung disease in the context of IPAH

Patients with PH due to lung disease have significantly poorer survival than patients with IPAH and PAH-CHD (94). Short term survival (less than 3 years) in patients with PH due to chronic lung disease (CLD-PH) is also worse than patients with PAH due to systemic sclerosis, although beyond three years

survival in CLD-PH is slightly better. Separating patients who have severe PH in the context of lung disease into either Group 1 or Group 3 represents a long-standing diagnostic challenge, and such patients have often been described as having PH "out of proportion" to lung disease, particularly when lung disease is not severe (95). Mild PH in patients with lung disease is common, but severe PH (defined as mPAP ≥35mmHg) is rare with a prevalence of approximately 10% (96-99).

The use of PAH targeted therapy in patients with CLD-PH is controversial and studies have identified conflicting results regarding treatment response. Some retrospective studies of patients with non-severe lung disease but severe PH have reported improved haemodynamics and exercise capacity following commencement of PAH therapies (100-102). Conversely, a retrospective registry analysis of patients at the Scottish Pulmonary Vascular Unit did not demonstrate an improvement in either 6-minute walk distance or functional class in 118 patients with varying degrees of lung disease and severe PH following the compassionate use of PAH-targeted therapy. Hurdman *et al* previously reported treatment response to PAH targeted therapy in less than 20% of patients with severe CLD-PH (103). There have also been prospective randomised controlled trials of PAH targeted therapies in patients with CLD-PH, but some of these have focused on using echocardiography rather than right heart catheterisation to measure pulmonary arterial pressures (104, 105). Other studies have assessed response to treatment in patients with only mild PH (106, 107), although a recent prospective study by Vitulo *et al* in a small cohort of patients with CLD-PH due to COPD with severe haemodynamics (n=31) showed improvements in pulmonary haemodynamics but not in exercise capacity (108). The role of PAH-targeted therapies in patients with chronic lung disease and severe PH remains unclear.

1.2.7 Exercise assessment in PAH

Exercise limitation is an early-presenting symptom in PAH, and regular assessment of exercise capacity is recommended in the ESC/ERS guidelines (18). Exercise capacity can be assessed by either field walking tests or cardiopulmonary exercise testing. The most widely used field walking test is the 6-minute walking test (6MWT) which, in early studies assessing PAH therapies, was demonstrated to be a marker of treatment response (86). Absolute distances are recognised to be prognostic, and deterioration of 6-minute walking test distance is strongly associated with poor prognosis (85, 109).

An alternative field walking test, the incremental shuttle walking test (ISWT), is used in our centre. It is used in other forms of cardiac and respiratory disease (110-112) and a number of recent studies from other centres have also highlighted its use in pulmonary hypertension (113, 114). Previous studies have demonstrated correlation between ISWT distance and haemodynamic parameters at right heart catheterisation (RHC) in PAH, and distances at baseline and follow-up predict survival (115).

Unlike the 6MWT, the ISWT is a maximal test and does not suffer from a ceiling effect (115, 116). Both the 6MWT and ISWT are inexpensive and simple to perform (115, 117, 118).

Cardiopulmonary exercise testing is regarded as the gold-standard for objective assessment of exercise capacity and provides a comprehensive evaluation of multi-organ response to physical effort (119). Parameters from CPET are associated with prognosis in PAH but its utility in routine clinical practice may be limited by cost, complexity and duration of procedure (120).

Thresholds for risk stratification for both 6MWT and CPET have been suggested, but no thresholds yet exist for the ISWT (18, 26).

1.2.8 Right Ventricular Function as a Marker of Prognosis

A common finding amongst risk stratification tools is the use of direct or indirect markers of right ventricular function. This provides important prognostic information, and right ventricular failure is recognised as the main cause of death in patients with PAH (121). As seen in massive pulmonary emboli, the right ventricle is poorly adapted to cope with acute increases in afterload and pressure due to its thin wall, however it is able to remodel in response to gradual increases in PVR (122). In PAH, patients with similar haemodynamics at baseline often have different outcomes, and it appears that how the right ventricle remodels and adapts to increased afterload is crucial (123). The ability to accurately assess and monitor right ventricle function at baseline and follow up is an important aspect of risk stratification. Right ventricular function may be measured directly using imaging modalities such as cardiac MRI or echocardiography, and cardiac output is typically measured invasively at right heart catheterisation although may also be assessed at cardiac MRI. Serum biomarkers may also provide indirect assessment of right ventricular function.

1.2.9 Blood biomarkers

There are a number of circulating serum biomarkers which are of interest in PAH. Natriuretic peptides (NPs) are a family of hormones secreted primarily from the heart, kidneys and brain that cause vasodilation and natriuresis. These primarily comprise atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). Compared to ANP, which is affected by temperature and has a short half-life, blood samples containing BNP are more stable and its half-life is approximately 22 minutes (124-126). N-terminal pro b-type natriuretic peptide (NT-proBNP) has an even longer half-life of approximately 70 minutes (126, 127). There has therefore been significant interest in BNP and NT-proBNP as clinical biomarkers.

Nagaya *et al* were the first group to demonstrate a link between right ventricular afterload and elevated levels of BNP, also identifying that it appeared more sensitive than ANP (128). They

subsequently demonstrated that elevated serum levels at diagnosis were an independent predictor of death in primary pulmonary hypertension, and also that patients with a rise in levels during follow up had a worse prognosis (129). Correlation with haemodynamics was confirmed by Leuchte *et al* who demonstrated that BNP levels rise in response to reduced 6MWD, cardiac index and peak VO_2 (130).

As a marker of right ventricular function, levels of BNP and NT-proBNP have been shown to have an inverse correlation with right ventricular ejection fraction (RVEF). A small study of patients with PAH (n=14) found a moderate inverse correlation between RVEF and BNP (r = -0.54), and RVEF and NT-proBNP (r = -0.61) (131). In another study of patients with PAH and CTEPH (n=25), a moderate inverse correlation (r = -0.66) between RVEF and NT-proBNP was identified (132). In congenital heart disease, a study of 21 patients who were either minimally symptomatic or asymptomatic with chronic right ventricular pressure overload also found that BNP levels inversely correlated with RVEF (r = -0.65) (133). Studies have also assessed response of these biomarkers to treatment in PAH, and changes in NT-proBNP have been shown to correlate with changes in metrics taken at cardiac MRI including right ventricular end-diastolic volume, right ventricular mass and RVEF (132, 134, 135). Both BNP and NT-proBNP are now widely used in the routine assessment of patients with PAH and guidelines suggest that there is no clear advantage of one over the other (43). Both BNP and NT-proBNP are incorporated into widely used risk stratification scores.

1.2.10 Recent developments in risk score calculators

It is increasingly recognised that no single marker can accurately prognosticate, and a wide number of markers have been proposed as outcome predictors in PAH. In the REVEAL registry, the authors identified variables which were associated with increased mortality at one year (26). As well as including non-modifiable factors, and underlying cause of PAH, modifiable risk factors were identified. A calculator was developed based on the above (Figure 4), although in the development cohort only 13.5% of patients were newly diagnosed with PAH, whereas the validation group consisted exclusively of incident patients. This may have been the cause of significant discordance between baseline variables.

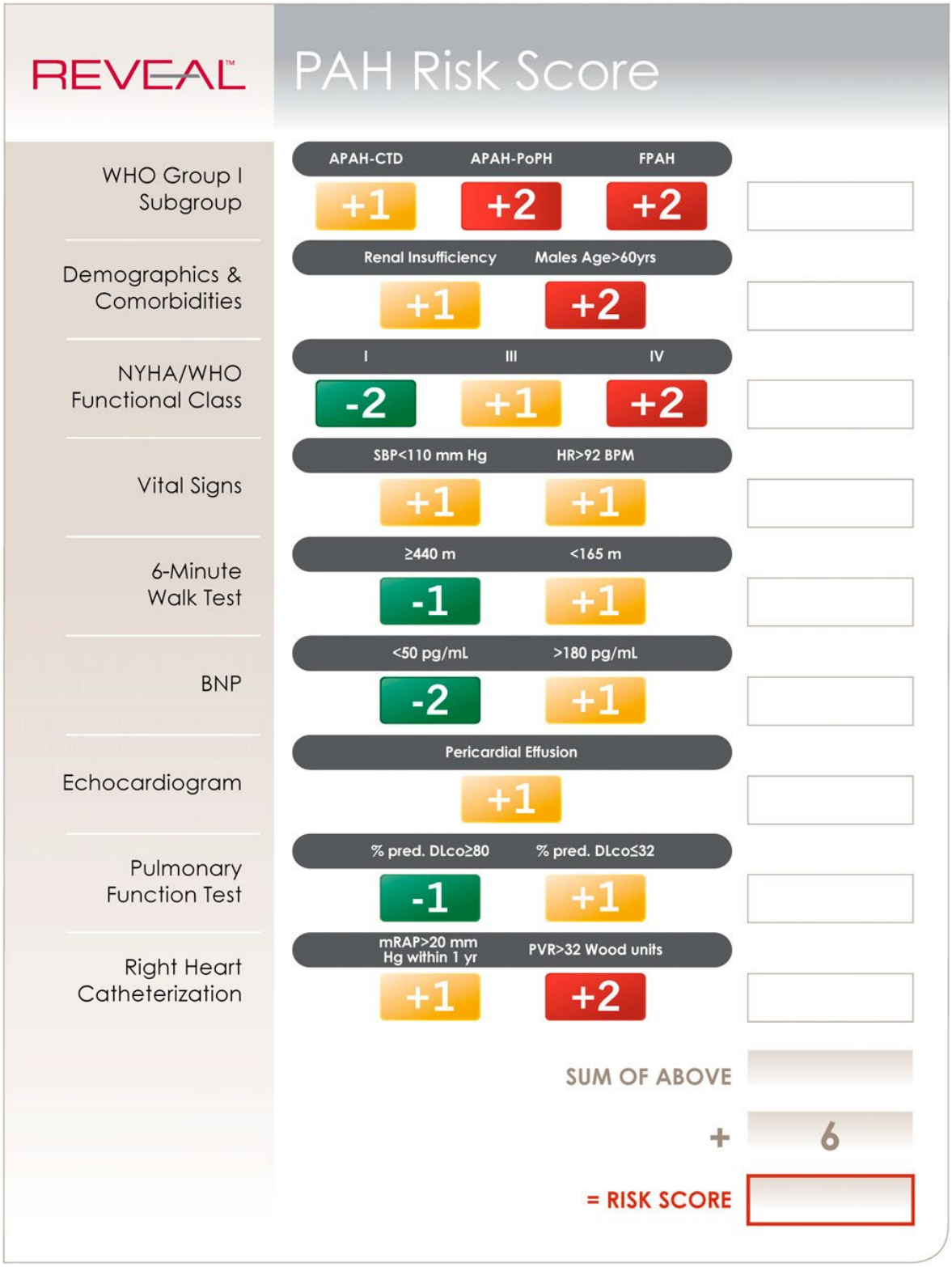

Figure 4: The REVEAL Risk Calculator. Reproduced from Benza et al (2012) with permission of the rights holder, Elsevier.

The original REVEAL risk score calculator attracted significant attention for a number of reasons, particularly as it has been robustly developed through statistical modelling on large population of

patients from a number of US centres, and allows risk assessment in all subtypes of PAH. This is in contrast to other risk score calculators which are only applicable in certain subtypes of PAH, such as IPAH or PAH-CTD. In the REVEAL risk score calculator, this has been facilitated by the addition of points for groups which are recognised to be high risk (particularly porto-pulmonary hypertension and heritable PAH), although it is important to note that that these comprised relatively small numbers in the REVEAL registry: in the validation cohort there were 13 (2.6%) patients with heritable PAH, and 34 (6.8%) patients with porto-pulmonary hypertension. While comprehensive, the wide range of investigations required in the REVEAL risk score calculator may make routine clinical use of this model challenging. The calculator does allow for missing data, though it is not suggested how many variables may be absent.

In addition to the REVEAL risk score calculator, there have been further attempts at producing accurate prognostic equations. Seeking to design a simple formula, Humbert *et al* prospectively followed 674 patients diagnosed between 2002 and 2003 with PAH for three years, although only published their findings in 2010 (88). They identified female sex, increased 6MWD and higher cardiac output were predictive of improved outcomes, and developed an equation predicting survival termed the French Pulmonary Hypertension Network (FPHN) predictive model.

In an effort to cross validate both REVEAL and the FPHN predictive models in independent populations, each model was applied retrospectively to the opposing population (136). In this study both models demonstrated reasonable discrimination: the c-statistic for the REVEAL equation was 0.73, and for the French Registry equation was 0.72. In addition, at Kaplan Meier analysis, survival using the REVEAL equation in the FPHN population demonstrated similar survival to that predicted by the model. The FPHN equation slightly under-estimated survival in the REVEAL population, where outcomes were slightly better than expected. This may relate to the time difference between model development and assessment in this study (a difference of approximately six years), as treatment regimens may have changed significantly over this time period due to the development of novel therapies (137).

1.2.11 REVEAL 2.0 risk score calculator

An updated version of the REVEAL risk score calculator (REVEAL 2.0) was developed and published in 2019 (138). In the development of the updated risk assessment tool, patients who had survived at-least one-year beyond diagnosis were included in the multi-variate model resulting in a number of changes to the initial REVEAL calculator. By including patients who had survived to at-least one-year beyond diagnosis, Benza *et al* were able to identify the previously unevaluated and negatively-prognostic variable of all-cause hospitalisation within the preceding 6 months. Renal insufficiency,

previously a semi-subjective assessment, was updated with an eGFR of <60 ml/min/1.73m^2, if laboratory data were available, and thresholds were changed for the modifiable variables of BNP/NT-proBNP, heart rate, 6MWD, PVR and DLco %pred. In addition, the number of points deducted for WHO functional class I symptoms was reduced, and the presence of porto-pulmonary hypertension scored an additional point. These changes resulted in a minor improvement in the predictive ability of the model, increasing the c-statistic from 0.74 (95% CI 0.72-0.76) to 0.76 (95% CI 0.74-0.78).

At present, only one validation study of the REVEAL 2.0 risk score calculator has been performed, which was undertaken in a cohort from the Pulmonary Hypertension Society of Australian and New Zealand (PHSANZ). A smaller subset of the entire registry was used, consisting of 1011 mixed incident and prevalent patients with greater than 7 variables available for analysis (139). Demographic data for the cohort were comparable to those in the REVEAL 2.0 validation cohort, with a very similar proportion of patients with IPAH (47% in PHSANZ vs 46% in REVEAL 2.0) although more patients with PAH-CTD (31% in PHSANZ vs 26% in REVEAL 2.0). In addition, the REVEAL 2.0 population was younger (mean age 54 vs 58) and had a slightly higher proportion of patients in WHO functional class I (8% vs 3%) and II (41% vs 39%), while exercise capacity as measured by 6MWD was similar (384m in PHSANZ vs 374m in REVEAL 2.0).

In this external validation, the c-statistic was identical (0.74) to the REVEAL 2.0 cohort and in a three-tier model of low, intermediate and high-risk there were significant differences for one-year mortality levels (2.6%, 8.6% and 25.4%, respectively).

This retrospective assessment of REVEAL 2.0 supports the validity of the risk score calculator. While there were missing data from patients in the study, one of the main strengths of REVEAL 2.0 is its development based on a heterogeneous population with only partially-available data, which improves its clinical usability in comparison with other risk stratification tools where the validity of such tools in the assessment of patients with incomplete data is unclear (140, 141).

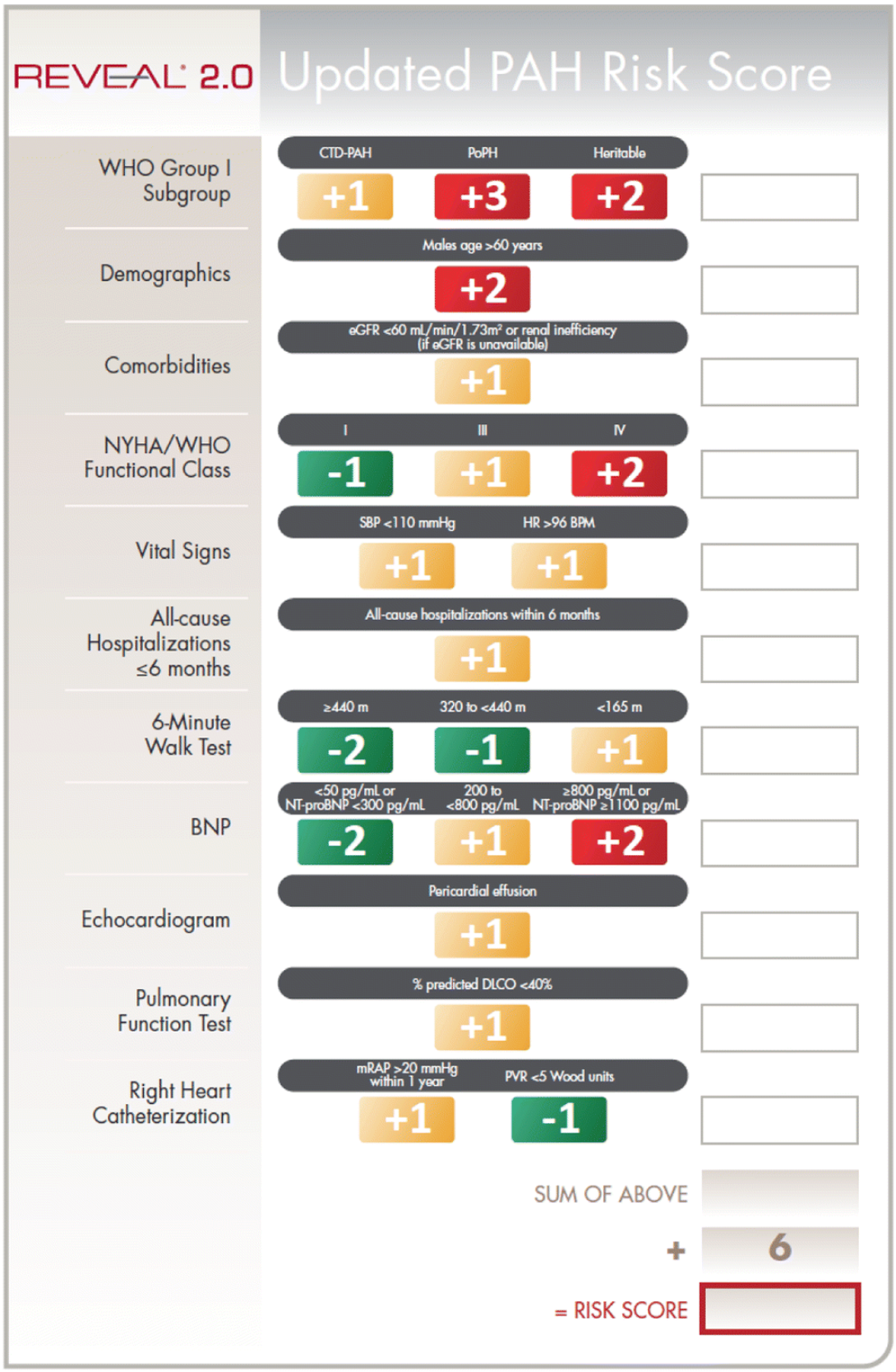

Figure 5: The REVEAL 2.0 updated risk score calculator. Reprinted without changes from Chest Journal, Benza et al, Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies, 2019, under the Creative Commons open access license agreement (CC BY-NC-ND 4.0) (138)

1.2.12 ESC/ERS Risk Stratification

In 2015, the European Society of Cardiology/European Respiratory Society (ESC/ERS) published guidelines for the diagnosis and assessment of patients with pulmonary hypertension (43). These guidelines were the first to feature tools for prognostic evaluation and risk stratification. In contrast to the REVEAL and REVEAL 2.0 risk score calculators, the prognostic parameters in the ESC/ERS guidelines were primarily based on expert opinion. Thresholds were suggested for routinely performed investigations at diagnosis and routine reassessment. Recognising that no single factor can predict outcome, they identify a goal of achieving a low-risk "profile". In a different methodology to other studies, Galiè *et al* proposed dividing risk outcomes into three categories based on risk of short term mortality, which has since been termed a traffic light assessment: low (<5%), intermediate (5-10%), and high-risk (>10%) of mortality at one-year (Table 2) (43). This approach does present some difficulties: it is unlikely that all of a patient's variables will fit into one of the risk thresholds, so application to individual patients is challenging. In addition, no weighting is given to each individual variable, but it is unlikely that they all confer equal risk. The authors do not provide references for the specific thresholds and acknowledge their reliance on expert opinion. To date, three large retrospective validation studies have been published and are discussed in further detail.

Table 2: Risk stratification model from ESC/ERS guidelines

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Abbreviations: WHO = World Health Organisation, 6MWD = six-minute walking test distance, NT-proBNP = N-terminal pro b-type natriuretic peptide, BNP = brain natriuretic peptide, CMR = cardiac magnetic resonance, VO_2 = oxygen uptake, VE = ventilation, vCO_2 = carbon dioxide uptake, RA = right atrial, RAP =right atrial pressure, CI = cardiac index, SvO_2 = mixed venous oxygen saturations.

1.2.12.1 Validation of the ESC/ERS Risk Stratification Tool

Kylhammar *et al* attempted to validate the ESC/ERS profile prognostication by retrospective registry analysis (142). The Swedish PAH Registry (SPAHR) consisted of 530 patients with Group 1 PAH, enrolled between 2008 and 2016. Retrospective registry analysis is often limited to some extent as new treatments may become available during the period of follow up which may affect results (137). In addition, follow-up regimes are not pre-defined as they are in prospective trials although conversely these less-rigid assessments may support the usage of such tools in a "real world" environment.

Subgroups of IPAH and other forms of PAH were analysed, and variables were assigned a score of 1-3 based on low, intermediate or high-risk. For individual patients these were summated and divided by the number of variables for each patient to provide an averaged or mean overall risk. As already identified, this strategy does have obvious weaknesses as it assumes equal weighting between variables. In addition, if few variables are available for individual patients then this may cause sampling error. In fact, there was no single variable available in all patients, either at baseline or follow up, for instance right atrial area was only available in 24% of patients at baseline, and cardiac index was

available in 33% at time of follow-up risk assessment. Data are not presented for the per-patient availability of variables. Nonetheless, allowing for these data availability issues, the study demonstrates that the proposed ESC/ERS profiling strategy accurately predicts risk at both baseline and follow-up when assessed in the same cohort of patients. This appeared to be true of IPAH and PAH-CTD; data are not given for other subtypes of PAH, but numbers are small which may have limited analysis. Of particular importance they successfully demonstrated that achieving a low-risk profile at follow-up produced the best outcomes. In clinical practice this may support the use of aggressive early treatment.

Hoeper *et al* provide the most comprehensive set of data for analysis by the ESC/ERS risk stratification (143). They assessed the risk profile in patients entered into the COMPERA registry between 2009 and 2016, which is a large European registry of patients with PAH. Of the variables and investigation modalities listed in the guidelines, a number were not available: history of syncope, history of disease progression, echocardiographic results and cardiopulmonary exercise test (CPET) data. In their abbreviated analysis, the authors therefore use six variables which were recorded in the COMPERA database consisting of WHO FC, 6MWD, either NT-proBNP or BNP, mRAP, cardiac index (CI), and mixed venous oxygen saturation (SvO_2). They identified 1588 patients who had at least two variables available for analysis, and 82.6% of patients had 5 of the 6 variables recorded at baseline. Using a similar methodology to the SPAHR approach, this study also calculated the mean score of available variables to assess risk profile and outcomes in patients established as low, intermediate or high-risk (142). The population consisted of 1060 (67%) with IPAH, HPAH or drug-associated PAH, 347 (22%) patients with PAH-CTD, 70 (4%) patients with PAH-CHD and 111 (7%) patients with other forms of PAH (143).

They demonstrated that, using this approach, the proposed ESC/ERS thresholds effectively stratified patients into low (<5%), intermediate (5-10%) and high (>10%) risk of mortality in patients with IPAH, HPAH and drug-associated PAH. In PAH-CTD the model was unable to discriminate between low and intermediate risk patients but did still identify those at high risk. As found in the studies by Boucly *et al* and Kylhammar *et al* the survival model appeared to work at both baseline and follow up assessment (28, 142). In keeping with the findings from the SPAHR study, this study also identified that patients whose risk profile had improved between baseline and follow up had significantly better outcomes than those whose risk profiles had not improved.

Boucly *et al* (28) applied the ESC/ERS criteria to the French Registry. In contrast to the SPAHR and COMPERA approach, they sought to identify specifically how achieving a low-risk profile affected outcomes. They used four criteria from the ESC/ERS guidelines: WHO FC, 6MWD, mRAP, and cardiac

index. These were assessed in a population of IPAH, heritable PAH and drug associated PAH at baseline and follow up (n=1017). The rationale for choosing these criteria is not presented, but presumably relates to availability of data. Defining a low-risk profile as consisting of three or four low-risk criteria, they identified that patients who had multiple low-risk criteria had better outcomes. Prognosis was not affected by which of the three low-risk criteria were present, suggesting that these variables may be similarly weighted. Achieving or maintaining a low-risk profile at follow-up conferred a one-year mortality risk of 0-1%. Those who had fewer than 3 low-risk criteria at baseline but improved to at least 3 criteria at follow-up had similar outcomes to those who maintained a low-risk profile from baseline. Patients who had one or more high-risk features and did not have any low-risk variables appeared to be compatible with the high-risk profile, with a one-year mortality of 13-30%. Intermediate-risk profile was difficult to characterise, which may relate to the large number of potential combinations. In a subgroup of patients with data available for WHO FC, 6MWD and either BNP or NT-proBNP (n=603), they demonstrated that a non-invasive assessment at follow-up also identified groups of patients with different outcomes.

Subsequently, Hoeper *et al* sought to identify whether they could replicate the results of the French approach, and applied the French risk assessment methodology to the COMPERA database (28, 141). They also demonstrated that having multiple low-risk criteria appeared to predict excellent long-term survival: using WHO-FC, 6MWD and BNP/NT-proBNP, they identified that patients with low-risk parameters for all three variables had 5-year survival of 95%. The mean age was higher in the COMPERA database compared to the French registry (64 vs 57), which may explain why fewer patients met three low risk criteria (9% vs 19%). Data from both of these studies assessing the role of non-invasive parameters in the routine follow-up of patients with PAH suggest that repeated haemodynamics are not necessarily routinely required at follow-up although some experts still recommend this (144).

In all of the validation studies, there were missing data when compared to the published ESC/ERS risk table. This is likely to be ubiquitous through all units and registries as clinician approach to investigation and management will differ based on experience and availability of investigations. Nonetheless these studies do demonstrate that even abbreviated scores using data obtained in routine clinical practice could effectively risk stratify patients.

There are a number of shortcomings shared by the ESC/ERS risk stratification tool and subsequent validation attempts. The risk assessment tool is primarily based on expert opinion, whereas ideally variables and parameters should be produced from a large and varied derivation cohort and undergo subsequent validation. None of the validation studies examined prevalent cohorts, although risk

profiles were reassessed in the same patient cohort at follow-up. All of the validation studies demonstrated good discrimination between patients at low and high-risk, but the large percentage of patients categorised as intermediate risk (70% in Hoeper *et al* and 67% in Kylhammar *et al*) and the inability of the model to discriminate well in this group suggests that further work is required in order to refine current risk stratification approaches (142, 143).

1.2.13 The Role of Imaging in Risk Stratification

As a modality, imaging is included in both the ESC/ERS guidelines and the REVEAL 2.0 risk score calculator, however it is limited to the detection of pericardial effusion (included in both risk assessment tools) and measurement of right atrial area (included only in the ESC/ERS guidelines). Neither pericardial effusion nor right atrial area has been included as a variable in any of the ESC/ERS validation studies. In addition, the data upon which inclusion of right atrial area was presumably based are relatively small, and the prognostic nature of this variable in addition to other risk stratification parameters is therefore unclear (56, 145). In both REVEAL 2.0 and the ESC/ERS the focus of risk assessment is upon the use of echocardiography, rather than more detailed metrics taken from cardiac MRI.

A number of studies have evaluated the role of cardiac MRI in PAH. As outlined previously, right ventricular function is an important prognostic marker, and deteriorating function strongly correlates with mortality in PAH. While echocardiogram remains the most commonly used investigation, cardiac MRI is now recognised as the gold standard in the assessment of right ventricular dimensions and function, even in congenital heart disease (146, 147). It has significantly better reproducibility than echocardiography making it potentially valuable in serial assessments. It also allows for a more comprehensive assessment of cardiac morphology than any other imaging modality, allowing measurement of blood flow, assessment of regurgitant valves and determination of systolic function without any restrictions relating to acoustic windows (147). As a research tool in the context of assessing novel treatments, the improved precision of cardiac MRI over echocardiography may mean that sample sizes in randomised control trials can be smaller, reducing the cost of developing new treatments (148). As an assessment in PAH, echocardiography is particularly limited by complex right ventricular structure and geometry (149), although some studies have shown a good correlation between assessment of right ventricular ejection fraction on cardiac MRI and markers of right ventricular function using echocardiography, including right ventricular fractional area change, which in one study of 36 patients with a spectrum of non-PAH disorders had a correlation coefficient of 0.8 (149).

A wide range of measurements can be taken at cardiac MRI, and a number of these have been proposed as important prognostic markers in PAH. As a cardiac MRI metric, right ventricular ejection fraction has received the most attention. This may in part be due to conceptual familiarity, given the widespread use of left ventricular ejection fraction in the cardiology community. In a multi-centre, heterogeneous cohort consisting of patients with PAH, CTEPH and PH due to lung disease, the EURO-MR study identified that RVEF significantly improved following the commencement of PAH targeted therapy (150). In a large study of 110 patients with PAH, an RVEF <35% was predictive of a poorer prognosis (151). Despite familiarity with RVEF, a number of other cardiac MRI biomarkers have been proposed.

Right ventricular stroke volume is an important marker in PAH and preserved stroke volume suggests that the right ventricle is able to cope with the increased afterload experienced in PAH. Reduced stroke volume has been associated with a high-risk of mortality (152, 153). In addition to its use as an isolated measurement, stroke volume may be used to estimate RV-PA coupling. Coupling is defined as the matching between right ventricular contractility and PA afterload, and has traditionally been calculated using pressure-volume loops and measurements of elastance from cardiac catheterisation (154). Such procedures are invasive, complicated and require conductance catheters, and increasingly it is recognised that coupling can be estimated from measurements obtained non-invasively, using stroke volume and end-systolic volume (155). In some studies these non-invasive measurements have been strongly associated with mortality, although other studies in larger cohorts have failed to show that coupling measurements have prognostic significance over simpler volumetric measurements (156, 157).

In a large study of patients with Group 1 PAH, Swift *et al* identified that volumetric measurements and measures of pulmonary arterial stiffness appeared to provide important prognostic value and specifically found that measurements of right ventricular volume and pulmonary artery relative area change were identified as strongly prognostic markers (157). An indexed right ventricular end-systolic volume has been identified as prognostic in a number of studies, although volumetric measurements of the left ventricle are also prognostic as it may become compressed in severe PAH by an enlarged right ventricle (151, 157). A dilated right ventricle is also prognostic in patients with left ventricular failure (158).

While raw MRI measurements can be useful, cardiac volumes are affected by age and sex and therefore adjusting MRI measurements for age and sex (expressed as percent predicted), and indexing for body surface area is recommended (159, 160). These corrected measurements are less convenient from a clinical perspective as adjusting for age, sex and body surface area is time consuming. This may

make calculated values less clinically useful, although some MRI software packages may be able to undertake these calculations automatically.

Nonetheless, there are some limitations with cardiac MRI and it remains an unsuitable imaging modality for some patients. Claustrophobia causes premature termination of scans in around 1-2% of patients (161, 162). Some patients are unable to undergo MRI due to metallic implants and devices such as pacemakers, which is an issue in the increasingly elderly and comorbid PAH population, although MRI conditional pacing systems may be fitted in patients in whom regular cardiac MRI follow-up is anticipated (163). Cardiac MRI is also a more expensive investigation than echocardiography (164). Furthermore, a range of MRI scanners and software packages are in use throughout hospitals and different sequences and protocols are used which may affect the reproducibility of measurements between difference centres. Standardising protocols between different centres would establish clinician confidence in this imaging technique and further encourage the uptake of cardiac MRI. In addition, normal values are not universally accepted for cardiac MRI parameters and different sets of normative data are available.

The ESC/ERS guidelines suggest repeated right heart catheterisation to assess haemodynamic parameters during follow-up in order to accurately prognosticate, however this is an invasive and resource-intensive procedure. Given the prognostic nature of cardiac MRI there is potential to non-invasively risk stratify patients at follow-up using the gold-standard measure of right ventricular function. There have, however, not been any direct studies to assess patient tolerance of cardiac MRI compared to right heart catheterisation and it is possible that some patients may prefer invasive rather than non-invasive follow-up, although it is likely that this represents a minority. The ability to non-invasively monitor the right ventricle over time and stratify by prognostic markers is therefore likely to be beneficial in PAH, but no study has yet looked at identifying predictive thresholds from candidate markers at cardiac MRI. For instance, it may be possible to identify thresholds for markers of right ventricular function or other cardiac MRI metrics that stratify patients into low, intermediate and high-risk of mortality in a similar manner to the ESC/ERS guidelines.

The reasons behind the current absence of cardiac MRI thresholds from existing risk stratification models are likely multi-factorial and relate to cost, availability, lack of widespread use and absence of thresholds for mortality. Nonetheless, it is well recognised to have a high degree of reproducibility and is validated for serial assessment of right ventricular function and, given the importance of right ventricular function in the prognosis of patient with PAH, further investigation into whether it can be used in risk-stratification is warranted (165). Cardiac MRI is potentially well-placed to form an integral part of risk assessment in patients with PAH, either as an individual test or as part of a wider algorithm.

1.3 Conclusion and Hypothesis

Comprehensive risk stratification is essential in pulmonary arterial hypertension due to the heterogeneity and varied course of the disease. While a number of attempts have been made to produce accurate modelling, these risk stratification tools provide modest predictive accuracy and often identify large cohorts of patients at intermediate risk in whom the optimal treatment strategy is unclear. There remains scope for further improvement upon current risk stratification approaches. Parameters at right heart catheterisation have been demonstrated as useful in prognostication, but the resource intensity and invasive nature of the test make this an unappealing investigation to undertake regularly during routine follow-up. The ideal risk stratification approach would primarily use non-invasive investigations, be accurate in incident and prevalent populations, and would be able to better delineate those patients at intermediate risk.

The presence of specific clinical phenotypes in patients with pulmonary hypertension, such as the presence of lung disease, also has a significant effect on outcomes and this should also be considered when assessing patients with pulmonary hypertension.

The overall hypothesis of this project is that non-invasive assessment of patients with pulmonary hypertension can identify distinct phenotypes and improve risk stratification.

Objectives

- To determine whether comorbid lung disease in patients with IPAH affects the risk profile
- To establish whether a threshold approach can be used for cardiac MRI and the incremental shuttle walking test to risk stratify patients with pulmonary arterial hypertension and assess their role in conjunction with other risk stratification tools
- To assess the role of health-related quality of life scoring as a prognostic tool in pulmonary arterial hypertension
- To assess whether improvements in maximal exercise capacity predict outcome in patients with pulmonary arterial hypertension

Whilst exploring relevant phenotypes it became apparent that the clinical phenotype of patients with partial anomalous pulmonary venous drainage had not been characterised and may have a bearing on outcomes. A preliminary evaluation of these patients was therefore performed and is included in this thesis.

1.4 Format of thesis

This thesis constitutes an “alternative format thesis” and consists of a literature review followed by five papers, which are either already published or submitted to journals for consideration of

publication, and these are followed by a summary discussion. In each of the five papers I have been the primary contributor.

In chapter 3, I designed the study in conjunction with the corresponding author, retrieved all data from clinical records and databases, performed radiological measurements on CT imaging, undertook all statistical analysis, wrote the first draft of the paper and, following suggestions from co-authors, wrote the final paper with input from the corresponding author.

In chapter 4, I designed the study in conjunction with the corresponding author, retrieved all data from clinical records and databases, in conjunction with others reviewed clinical notes to assess extent of lung disease, undertook all statistical analysis, wrote the first draft of the paper and, following suggestions from co-authors, wrote the final paper with input from the corresponding author.

In chapter 5, I designed the study in conjunction with the corresponding author, retrieved all data from clinical records and databases, undertook the vast majority of statistical analysis (the LOESS regression was performed by a statistician), wrote the first draft of the paper and, following suggestions from co-authors, wrote the final paper with input from the corresponding author.

In chapter 6, I designed the study in conjunction with the corresponding author, retrieved all data from clinical records and databases, undertook all statistical, wrote the first draft of the paper and, following suggestions from co-authors, wrote the final paper with input from the corresponding author.

In chapter 7, I designed the study in conjunction with the corresponding author, retrieved all of the SPVDU data from clinical records and databases and collated all data provided by other centres in a variety of formats, undertook all statistical analysis, wrote the first draft of the paper and, following suggestions from co-authors, wrote the final paper with input from the corresponding author.

The papers are presented in the format in which they were submitted to the journals, apart from minor formatting changes and abbreviations to provide consistency throughout the thesis.

2. Methods

2.1 Introduction

Pulmonary arterial hypertension is a rare disease. For adults in the United Kingdom, management and treatment of this condition is limited to the National Pulmonary Hypertension Service, which consists of eight specialist centres. The Sheffield Pulmonary Vascular Disease Unit (SPVDU) investigates and treats patients from a wide area consisting of North Wales, the Midlands, Manchester, Liverpool, the North West, Lincolnshire and Yorkshire. It is the largest pulmonary hypertension referral centre in the UK, and one of the largest individual centres in the world, with a catchment population of 15 million (166). This provides SPVDU with a large volume of data for a relatively rare disease.

Patients who are newly referred are usually seen in an outpatient clinic initially to determine the likelihood of pulmonary hypertension. Based on the clinical features, assessment of previous imaging and usually with the results of an echocardiogram, patients are brought back as a day-case for further assessment. At this time patients undergo multi-modality assessment to determine the severity of pulmonary hypertension and any likely underlying cause. Typical investigations include electrocardiogram (ECG), lung function testing, exercise testing in the form of incremental shuttle walking test (ISWT), computed tomography (CT) imaging of the chest (usually contrast-enhanced), cardiac MRI (and magnetic resonance angiography (MRA) if chronic thrombo-embolic pulmonary hypertension is suspected), isotope perfusion lung scan (Q scan) and right heart catheterisation. Patients are evaluated by a consultant clinician, and all new diagnoses are discussed in the pulmonary vascular multidisciplinary team (MDT) meeting to ensure a standardised diagnosis.

Patients without pulmonary hypertension, or those in whom pulmonary hypertension is due to lung disease or left heart disease (and as such will not benefit from targeted pulmonary vasodilator therapy), are discharged from further follow-up. Patients with pulmonary arterial hypertension are commenced on appropriate treatment and kept under regular follow-up. Patients with chronic thrombo-embolic pulmonary hypertension are referred to the national pulmonary endarterectomy service at Royal Papworth Hospital for an assessment as to whether surgery is appropriate, and are commenced on treatment if necessary. Those who are not suitable for surgical intervention are usually commenced on treatment and kept under regular follow-up. Those who undergo surgery are usually followed-up for a minimum of five years after surgery, and longer if there is residual pulmonary hypertension.

2.1.1 Follow up

Follow-up appointments consist of subjective and objective assessment of pulmonary vascular status, including a patient-reported outcome measure (PROM) to assess symptom burden (emPHasis-10 score), a clinician assessment of symptom burden (WHO Functional Class), a measure of exercise capacity in the form of ISWT, and an assessment of right ventricular function. This is typically undertaken by NT-proBNP testing, but this has only recently become accessible for clinical use, and results are not available for the patient population under assessment in this study. An alternative measure of right ventricular function is cardiac MRI, which in this study has been the primary investigation used for follow-up assessment of right ventricular function. Cardiac MRI is a time-consuming and expensive investigation and access is therefore limited. In our centre it is used routinely in the follow-up assessment of patients with idiopathic PAH, and patients typically undergo serial assessment every one to two years. It is also used in patients who are suspected to have had clinical deterioration, or where the cause of clinical deterioration is unclear and warrants direct assessment of right ventricular function.

2.1.2 Investigations and assessments

2.1.2.1 Database interrogation and data integration

Data from baseline and follow-up investigations are stored electronically. A number of different computer database packages are in use in our centre. Most clinical data are stored on the Infoflex system, which records patient demographics, diagnosis data and results from the majority of investigations. Mortality data were obtained from the NHS Personal Demographics Service which is linked to Infoflex. Some older data (pre 2012) from the respiratory function unit consisting lung function and exercise testing are stored on a separate clinical database called ArQ, and some data were taken from the ASPIRE database. Blood test results were downloaded from Sunquest ICE. All clinically sensitive information was accessed on secured NHS computers and de-identified. Data from these sources were then combined, primarily using Microsoft Excel, and subsequently exported to SPSS for analysis.

2.1.2.1 Statistical analysis

Statistical analysis was performed using SPSS (IBM) v25 and v26, GraphPad Prism v8 and R software. Unless otherwise specified, all statistical analysis was performed by RL and statistical advice was sought, where required, from experienced statisticians at the University of Sheffield. Figures were developed in SPSS, GraphPad Prism and Adobe Illustrator 2019. Continuous data were typically presented as either mean ± standard deviation for normally-distributed data, or median (first quartile, third quartile) for non-parametric data. Comparison between groups was performed using paired or

unpaired T-Tests for normally-distributed data, and Mann-Whitney or Wilcoxon signed rank test for non-parametric data. Categorical data were compared using χ^2.

Multivariate analysis was performed in a forward step-wise direction on variables with a *p* value <0.2 at univariate analysis. For all other statistical tests, a *p* value <0.05 was considered statistically significant.

A number of census dates were used and these are described in the individual chapters.

2.1.2.1.1 Specific statistical methods in chapter 4

In chapter 4, several options were considered to identify thresholds for cardiac MRI parameters. One of the challenges of using cardiac MRI imaging in patients with PAH is the absence of studies that identify thresholds for specific metrics that could be used in clinical practice to risk stratify patients with PAH according to the ESC/ERS guidelines. For other non-MRI metrics used to risk stratify patients using this guideline approach, arbitrary thresholds were established based on expert opinion. Subsequent studies then assessed these arbitrary thresholds. Based on the absence of expert opinion or consensus regarding specific MRI thresholds for risk stratification, the purpose of this study was to establish thresholds in a discovery cohort and assess the performance of these thresholds in a test cohort.

Based on the number of patients in this study and the number of events, and following statistical advice[1], it was felt that using five groups to establish thresholds in the discovery cohort was preferable to 10 groups. In the discovery cohort, patients were divided into five groups: subjects were ranked in ascending order for each variable, and split into quintile groups with an equal number of patients in each group. Mortality was analysed in each quintile group. Where contiguous groups shared the same risk level (<5%, 5-10%, >10%) these were combined, reducing the number of thresholds to either one or two, thereby creating two or three categories of risk.

To provide a confirmatory assessment of thresholds a locally weighted estimated scatterplot smoothing (LOESS) regression was undertaken[2].

[1] Statistical advice was provided by Kathleen Baster and Pete Laud, School of Mathematics and Statistics, University of Sheffield

[2] The R code for LOESS regression curves was provided by Pete Laud, School of Mathematics and Statistics, University of Sheffield

2.1.2.2 Quality of life scores

Quality of life and patient-reported outcome measures (PROMs) are increasingly recognised as an important assessment in PAH (167). Three PAH-specific PROMs exist: the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT), and emPHasis-10. Since 2014, all centres in the UK record regular patient-reported quality of life scores and in our unit emPHasis-10 scores are recorded at each visit.

2.1.2.3 Pulmonary function testing

Spirometry and lung function tests were performed at, or prior to, diagnosis in a dedicated laboratory on the pulmonary vascular unit by respiratory physiologists.

2.1.2.4 Incremental Shuttle Walking Test

The incremental shuttle walking test (ISWT) is a field walking test used to objectively measure exercise capacity in respiratory disease. The ISWT was performed as described by Singh *et al* (168). Patients walk between two cones placed 9m apart, with 0.5m allowed at each end for turning (Figure 6). The total distance of 10m is termed one shuttle. There are 12 levels in total, with an increasing number of shuttles in each level. Patients are required to keep up with an external pacer beep, which starts off slowly. Initially patients have 20 seconds to complete a shuttle (a required speed of 0.5m/s), but this speed increases every level. The test is discontinued when the patient it unable to keep up with the required pace or when they become too breathless to continue. It is possible to complete the test, which is a total distance of 1020m, and requires a pace of 2.37m/s.

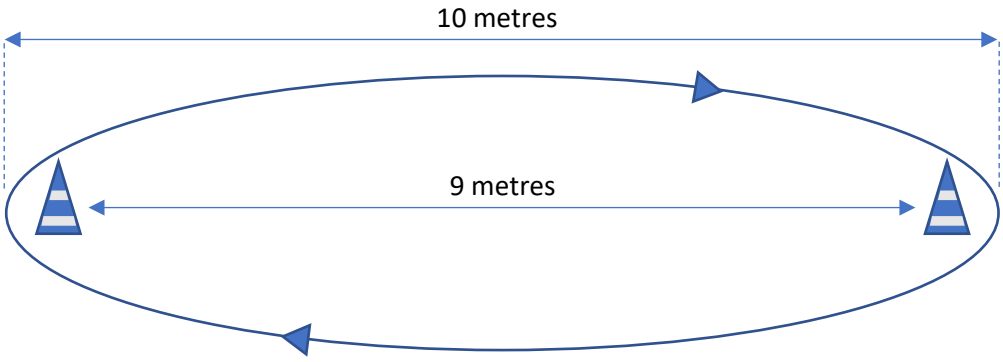

Figure 6: Layout of the incremental shuttle walking test

2.1.2.5 Computed tomography (CT) scans

Patients who are assessed for pulmonary hypertension usually undergo contrast-enhanced CT scans. These scans provide important information on features of pulmonary hypertension including pulmonary artery diameter, evidence of right ventricular outflow tract hypertrophy, cardiac chamber

size and evidence of interventricular septal deviation (169). In addition, CT scans allow assessment of lung parenchyma, exclusion of thrombo-embolic disease and assessment of pulmonary venous drainage and interatrial communications (170).

2.1.2.1 Right heart catheterisation

Cardiac catheterisation was performed by experienced operators using a balloon-tipped 7.5 Fr thermodilution catheter, with the patient in the supine position. Catheters were inserted under sterile conditions using ultrasound guidance, and were positioned using fluoroscopy. Cardiac output was measured by the thermodilution technique. Where appropriate, a vasodilator challenge was performed using inhaled nitric oxide to assess for vasoreactivity. A positive vasodilator response was defined as a drop in mPAP by ≥10mmHg to a value ≤40mmHg without a fall in cardiac output (46).

2.1.2.2 Cardiac MRI and image acquisition

Cardiac cine MRI was performed on a 1.5T GE HDx MRI scanner using an 8 channel receiver array and multi-slice balanced steady state imaging with retrospective gating (20 frames/cardiac cycle; slice thickness 8 mm; field of view 48; matrix 256 x 256; band width 125 kHz/pixel; repetition time/echo time TR/TE, 3.7/1.6 ms). A stack of images in the short-axis plane with slice thickness of 8 mm, 2mm inter-slice distance) were acquired covering both ventricles from base to apex. End-systole was considered to be the smallest cavity area. End-diastole was defined as the first cine phase of the R-wave triggered acquisition or largest volume.

Image analysis was performed by operators blinded to diagnosis and cardiac catheter result. Endocardial and epicardial surfaces were manually traced on short axis imaging to obtain end-systolic and end-diastolic volumes for the right ventricle (RVESV, RVEDV) and left ventricle (LVESV, LVEDV); Figure 7. Trabeculations for the chambers were not separately traced, and were included as part of the volume cavity measurement (171). Right ventricular ejection fraction (RVEF) was calculated from these volume measurements as previously described (157). Volumes were indexed for body surface area (RVESVi, RVEDVi, LVESVi, LVEDVi), and then corrected for age and sex and displayed as percent-predicted (%pred), as previously described (159). Ventricular mass index was calculated as right ventricular mass divided by left ventricular mass (172). Pulmonary artery relative area change (RAC) was measured on the magnitude images of phase contrast images and was calculated as (maximum pulmonary arterial area – minimal pulmonary arterial area)/minimal pulmonary arterial area. Phase contrast imaging parameters were as follows: repetition time TR/TE 5.6/2.7 ms; slice thickness 10 mm; field of view 48 cm, bandwidth 62.5 kHz; matrix 256 3128; 40 reconstructed cardiac phases; and velocity encoding of flow 150 cm/s. Patients were in the supine position with a surface coil and with retrospective ECG gating.

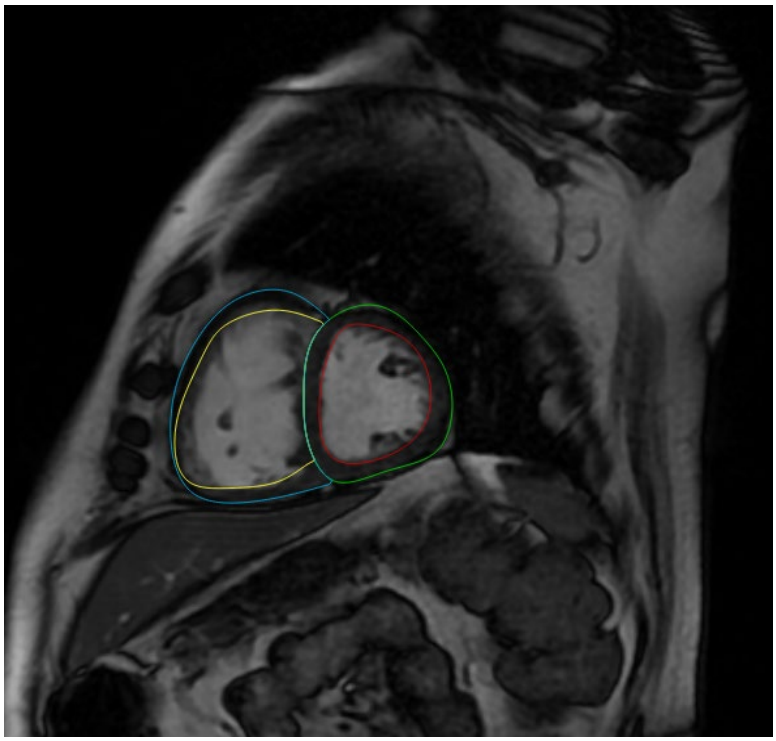

Figure 7: Contouring of cardiac border at MRI during diastole. Blue and yellow contours: RV epicardial and endocardial surfaces. Green and red contours: LV epicardial and endocardial surfaces

2.1.2.3 Ethical approval

Ethical approval for individual projects and for use of the ASPIRE database was granted by Sheffield Teaching Hospitals NHS Foundation Trust (STH 14169), and was approved by the NHS Research Ethics Committee (16/YH/0352). In chapter 7 ethical approval was granted by the Health Research Authority (HRA). Specific NHS research ethics was not required as data from all centres were de-identified prior to analysis (IRAS 254446).

3. Partial anomalous pulmonary venous drainage in patients presenting with suspected pulmonary hypertension: a series of 90 patients from the ASPIRE registry

Respirology. 2020 *(in press)*

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Key words: Pulmonary hypertension, anomalous pulmonary venous drainage

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3.1 Abstract

Introduction. There are limited data regarding patients with partial anomalous pulmonary venous drainage (PAPVD) with suspected and diagnosed pulmonary hypertension (PH).

Methods. Patients with PAPVD presenting to a large PH referral centre during 2007-17 were identified from the ASPIRE registry.

Results. Ninety patients with PAPVD were identified; this was newly diagnosed at our unit in 71 (78%) despite 69% of these having previously undergone computed tomography. Sixty-seven percent had a single right superior and 23% a single left superior anomalous vein. Patients with a sinus venosus atrial septal defect (SV-ASD) had a significantly larger right ventricular area, pulmonary artery and left-to-right shunt and a higher %predicted DLco (p all <0.05). Sixty-five patients were diagnosed with PH (defined as mean pulmonary arterial pressure ≥25mmHg), which was post-capillary in 24 (37%). No additional causes of PH were identified in 28 patients; 17 of these (26% of those patients with PH) had a pulmonary vascular resistance >3 WU. Seven of these patients had isolated PAPVD, 5 of whom (8% of those patients with PH) had anomalous drainage of a single pulmonary vein.

Conclusion. Undiagnosed PAPVD +/- ASD may be present in patients with suspected PH; cross-sectional imaging should therefore be specifically assessed whenever this diagnosis is considered. Radiological and physiological markers of left-to-right shunt are higher in patients with an associated SV-ASD. Although many patients with PAPVD and PH may have other potential causes of PH, a proportion of patients diagnosed with PAH have isolated PAPVD in the absence of other causative conditions.

3.2 Introduction

Anomalous pulmonary venous drainage (APVD) describes a pattern where one of more of the pulmonary veins do not drain into the left atrium but instead are connected to the right atrium, superior or inferior vena cava, azygous vein, coronary sinus or brachiocephalic vein. The prevalence of APVD in adults was found to be 0.1% in a large study involving 45,538 consecutive thoracic computed tomography (CT) scans (173).

Total APVD presents early in life with neonatal distress and circulatory compromise. Partial anomalous pulmonary venous drainage (PAPVD) may present later in life due to symptoms related to a volume-loaded right ventricle (as a result of left to right shunting, L-R) or subsequent development of pulmonary arterial hypertension (PAH) (18, 174). Alternatively, patients may remain asymptomatic and PAPVD be diagnosed incidentally. PAPVD is commonly associated with other congenital heart defects, particularly sinus venosus atrial septal defects (SV-ASD) (175-178). Once diagnosed, management of patients with PAPVD may involve surgical correction, may be conservative or may involve medical therapy (174).

Due to right ventricular dilatation resulting from left-to-right shunting and/or the development of pulmonary hypertension (PH), patients with PAPVD may present to PH referral centres but there are few published data regarding patients with suspected or proven PH and co-existing APVD. We therefore performed a study to assess patients with PAPVD presenting to a large PH referral centre over a ten-year period.

3.3 Methods

Records for all patients seen at a large PH referral centre between 2007 and 2017 were assessed for evidence of APVD. Hospital databases, including the ASPIRE (Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre) registry and electronic medical records, were interrogated for keywords including “anomalous”, “pulmonary venous drainage”, “pulmonary venous return”, “scimitar” and “sinus venosus”. Patients who had undergone corrective surgery for PAPVD prior to being seen were excluded, as were those whose cases had been referred or discussed, but not formally seen at our centre. Data regarding associated structural abnormalities, comorbidities, pulmonary haemodynamics and mortality status at the census date of 31st May 2017 were collected. Pulmonary venous anatomy had been assessed on CT imaging (contrast-enhanced in 88 patients). Cardiac chamber area, pulmonary arterial and aortic diameter were subsequently measured by one author (RL), blinded to clinical details. Cardiac magnetic resonance imaging had been performed in a

proportion of patients; pulmonary to systemic shunt assessments (Qp:Qs) derived from phase contrast flow measurements were retrieved. Spirometry was available for 97% and percent-predicted diffusing capacity for carbon monoxide (DLco %pred) for 89% of patients. At cardiac catheterisation, cardiac output was measured by thermodilution. Pulmonary hypertension was defined as mPAP ≥25mmHg, in keeping with the definition at the time of study enrolment.

Patients with uncorrected PAPVD who had undergone corrective surgery for an atrial septal defect (ASD) were included in the study but were excluded from comparison against patients with isolated PAPVD. Regional adult congenital heart disease (ACHD) centres were contacted to establish whether patients seen at our centre had subsequently received any surgical intervention for PAPVD or ASD.

Statistical analysis was performed using SPSS v25 (IBM) and GraphPad Prism v8. Continuous data were presented with mean ± standard deviation. Comparison between groups was performed using the unpaired T-test and response to treatment using the paired T-test. A p-value of <0.05 was considered significant.

Approval by the relevant ethics committee was sought and gained (STH14169, NHS Research Ethics Committee 16/YH/0352), and written consent was waived.

3.4 Results

Demographics

Ninety patients with PAPVD were identified from our departmental databases. Demographics and haemodynamic and radiological data are displayed in Table 3. Hemodynamic data are displayed visually in Figure 8. The majority of patients were female (70%) with a mean age of 60.

Table 3: Baseline Demographics

Age (years)	60.4 ±15.2
Gender (%female)	70
WHO Functional Class I/II/III/IV (%)	0/24/68/8
Lung Function	
FEV_1 (%pred)	70.4 ±20.5
FVC (%pred)	85.0 ±22.4
FEV_1/FVC (%)	68.3 ±11.4
DLco %pred	73.5 ±23.6
ISWD (m)	227 ±166
Haemodynamics	
mRAP (mmHg)	11 ±7
mPAP (mmHg)	39 ±15
PAWP (mmHg)	14.0 ±7.0
CO (L/min)	5.9 ±1.9
CI (L/min/m^2)	3.2 ±0.9
PVR (WU)	4.8 ±3.8
PVRi (WU.m^2)	8.4 ±6.3
PA saturations (%)	78 ±8
Anatomical Defect (%)	
Right superior vein	66.7
Total right	4.4
Left superior vein	23.4
Right and left superior vein	4.4
Total left	1.1

WHO = World Health Organisation. FEV1 = Forced expiratory volume in 1 second, FVC = forced vital capacity, DLco = diffusion capacity for carbon monoxide, ISWD – incremental shuttle walking test distance.Haemodynamics measured at right heart catheterisation: mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, CO = cardiac output, CI = cardiac index, PVR = pulmonary vascular resistance, PVRi = pulmonary vascular resistance indexed for body surface area, PA = pulmonary arterial

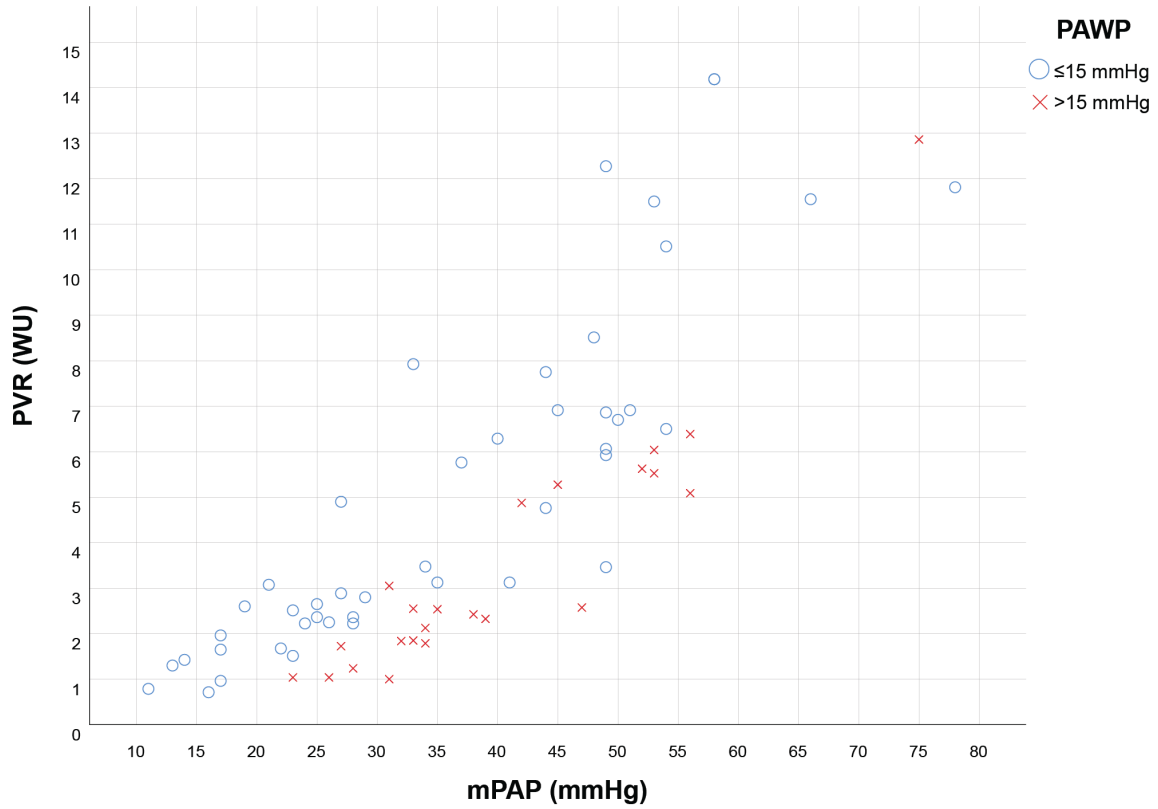

Figure 8: Scatter plot demonstrating haemodynamic parameters for patients with PAPVD, categorised by PAWP ≤15 mmHg (circle) and >15mmHg (x).

Abbreviations: PVR = pulmonary vascular resistance; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PAPVD = partial anomalous pulmonary venous drainage.

Pulmonary venous anatomy

Seventy-one patients (79%) were newly diagnosed with PAPVD following review at the unit; 49 of these 71 patients (69%) had previously undergone contrast-enhanced CT locally where the anomalous venous drainage had not been appreciated. A SV-ASD was visible on cross-sectional imaging in 31 patients (34%); the SV-ASD had not been previously diagnosed in 25 (81%) of these (Figure 9). PAPVD was isolated (i.e. there was no evidence of an associated ASD) in 47 patients. Six further patients had previously undergone ASD repair but still had PAPVD.

The majority of patients had abnormal drainage limited to the right superior vein (n=60; 67%, Table 3). Of these, 44 had isolated right upper lobe abnormal drainage while 16 had combined right upper and middle lobe abnormalities. Twenty-one patients (23%) had an isolated left superior vein anomaly. Five patients (6%) had anomalous connection of an entire lung; the right lung was affected in 4 patients, and the left lung in 1 patient.

Pulmonary Haemodynamics

Eighty patients (89%) underwent right heart catheterisation (RHC) and 64 (79% of those undergoing RHC) were found to have PH as defined at the time of study enrolment by a mean pulmonary arterial pressure (mPAP) ≥25mmHg. A further patient with Eisenmenger physiology did not undergo RHC. PH was post-capillary (as defined by a pulmonary arterial wedge pressure (PAWP) >15mmHg) in 24 (37%) patients.

Measurement of pressure in the wedged position of the pulmonary artery supplying lung with anomalous venous drainage will actually measure right atrial pressure. As the lobe in which the PAWP was measured was not recorded at the time of catheterisation we therefore compared the left atrial (LA) area, measured on CT, of those with a PAWP of ≤15 mmHg and >15 mmHg. LA area was significantly larger (31.4cm^2 vs 20.1cm^2, $p<0.0005$) in patients with a PAWP >15mmHg.

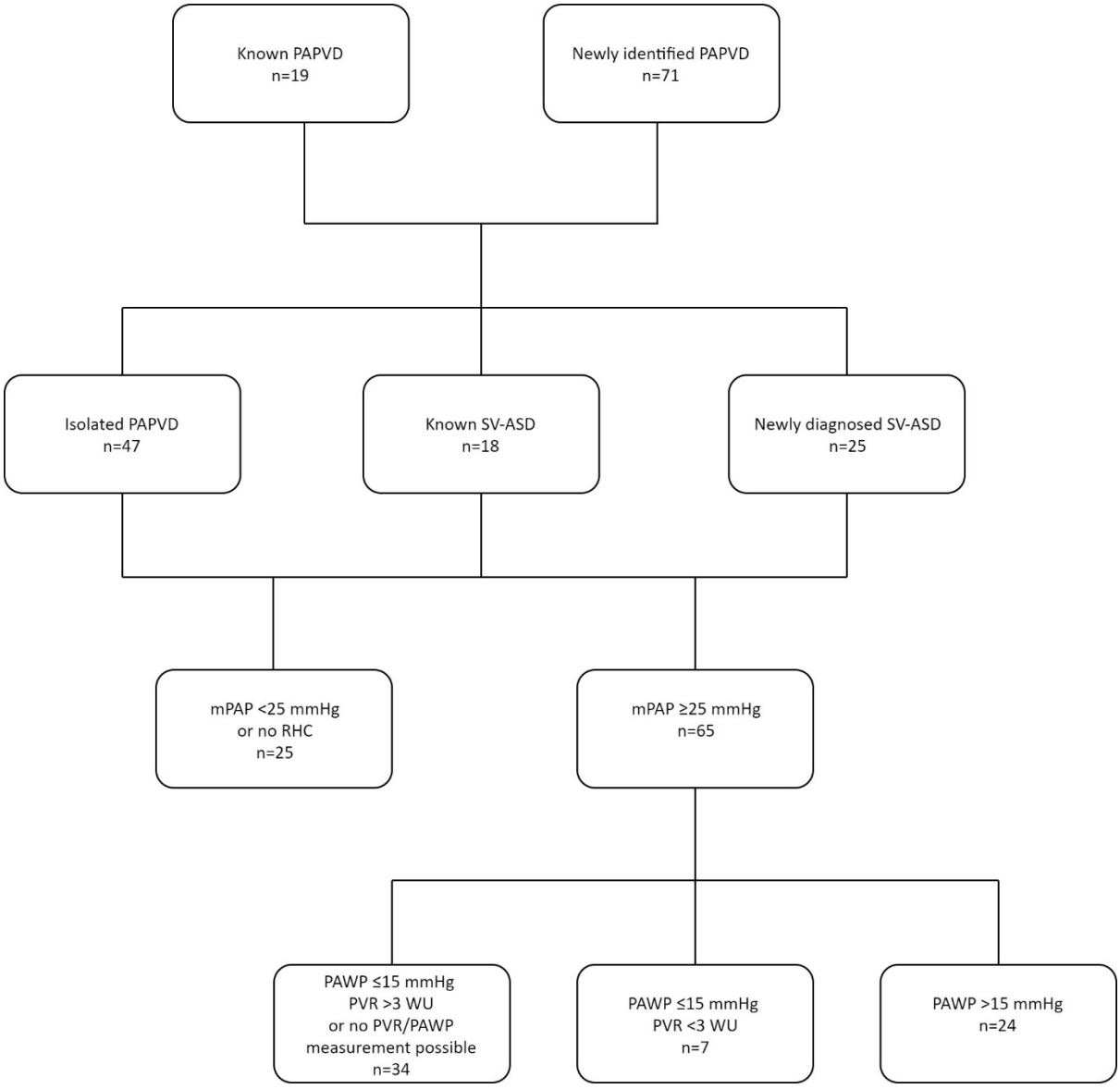

Figure 9: Flow chart demonstrating frequency of SV-ASD and haemodynamic parameters in patients with PAPVD.

Abbreviations: PAPVD = partial anomalous pulmonary venous drainage; SV-ASD = sinus venosus atrial septal defect; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance.

Cardiac anatomy

Cardiac chamber measurements for patients who had isolated PAPVD compared with those with an associated ASD are displayed in Table 4. Patients with isolated PAPVD had a smaller right ventricular area (31.6cm^2 vs 38.6cm^2; p=0.001). There was no significant difference for left atrial area (22.8cm^2 vs 22.9cm^2) or right atrial area (30.8cm^2 vs 33.0cm^2 respectively) between the two groups. Patients with an associated ASD did, however, have a larger pulmonary artery diameter (3.9cm vs 3.4cm, p=0.003). Right atrial, right ventricular (RV) and LA areas were larger in patients with an elevated PAWP (p all <0.01) while there was a trend towards a larger pulmonary artery in those with an elevated PAWP (p=0.053).

Shunt data

Qp:Qs as assessed by flow measurements at cardiac MRI, performed in 43 patients, was significantly higher in patients with an associated SV-ASD compared to those without (2.2:1 vs 1.5:1; p=0.006). Percent-predicted DLco was significantly higher in patients with an associated SV-ASD (81% vs 67%; p<0.05). There was no significant difference in cardiac MRI-derived Qp:Qs between those patients with a normal versus an elevated PAWP.

Single versus multiple anomalous pulmonary venous drainage

In those with isolated PAPVD, both Qp:Qs measured at cardiac MRI and DLco %pred were higher (1.8:1 vs 1.3:1 and 83% vs 63%, respectively, p both <0.05) in those with anomalous pulmonary veins draining >1 lobe. A mPAP ≥25 mmHg was observed in 27 patients with isolated anomalous drainage of a single pulmonary vein. Of these patients, 17 (63%) had a PVR >3 WU.

Comorbidities

Additional possible causes of PH were present in 37 out of the 65 patients with PH (57%): elevated left atrial pressure (n=18), significant lung disease (n=8), combined elevated left atrial pressure and lung disease (n=4), chronic thromboembolic disease (n=4), cirrhosis (n=2) and hereditary haemorrhagic telangiectasia (n=1). One patient with chronic thromboembolic disease and one patient with cirrhosis also had an elevated PAWP. No additional causes of PH were identified in 28 patients (43%). Seventeen of these 28 patients (26% of those patients with PH) had a PVR >3 WU. Seven (11% of those with PH)

of these patients had isolated PAPVD, 5 of whom (8% of those patients with PH) had anomalous drainage of a single pulmonary vein.

Follow-up and outcomes

By the census date, 16 patients (18%) had died. Fifteen patients were already known to congenital heart disease units prior to being seen at our centre. Fifty-three patients were subsequently referred by ourselves to regional adult congenital heart disease centres for assessment for re-routing of anomalous pulmonary veins and/or closure of ASDs. Fifteen patients were identified as being appropriate for surgical intervention (mean mPAP 28 ±8 mmHg, mean PAWP 11 ±4 mmHg, PVR 2.6 ±0.9 WU) and 13 chose to have surgical correction performed. Eleven of these fifteen patients had an associated SV-ASD with 3 of the 4 patients without a SV-ASD having abnormal drainage of >1 pulmonary vein. Twenty-nine PH patients (mean mPAP 50 ±9 mmHg, mean PAWP 10 ±4 mmHg, PVR 8.4 ±3.5 WU) received a trial of PAH therapy (phosphodiaesterase-5 inhibitor, n=19; endothelin receptor antagonist, n=4; oral combination therapy, n=2 and prostanoid-based therapy, n=4). Mean improvement in incremental shuttle walking distance from baseline to first follow-up in the 25 patients with follow-up data following initiation of PAH therapy was 23m (p=0.2).

Table 4: Comparison of patients with isolated PAPVD and PAPVD + ASD*

	Isolated PAPVD (n=47)	**PAPVD and ASD (n=37)**	***p* value**
CT Measurements			
Aorta (cm)	3.1 ±0.5	3.0 ±0.5	0.286
PA (cm)	3.4 ±0.6	3.9 ±0.7	0.003
LA (cm^2)	22.8 ±9.3	22.9 ±7.0	0.956
RA (cm^2)	30.8 ±14.3	33.0 ±12.6	0.495
RV (cm^2)	31.6 ±8.5	38.6 ±8.5	0.001
Qp:Qs (Cardiac MRI)**	1.5 ±0.4 :1	2.2 ±0.9 :1	0.006
DLco %pred	67.4 ±24.1	80.6 ±20.7	0.015
Haemodynamics			
mRAP (mmHg)	10.9 ±6.4	10.1 ±6.3	0.609
mPAP (mmHg)	36.7 ±15.5	41.4 ±15.7	0.209
PAWP (mmHg)	13.2 ±6.5	13.1 ±7.1	0.955
CO (L/min)	5.9 ±2.0	5.9 ±1.7	0.962
CI (L/min/m2)	3.2 ±1.0	3.3 ±0.8	0.559
PVR (WU)	4.8 ±3.9	4.7 ±3.2	0.868
PVR ($WU.m^2$)	8.9 ±7.4	8.5 ±5.0	0.791
PA saturations (%)	76 ±8	80 ±7	0.064

**Patients with a previously closed ASD were not included in this analysis.*

*** 43 patients had data available from cardiac MRI*

Abbreviations: PA = pulmonary artery, LA = left atrium, RA = right atrium, RV = right ventricle, Qp:Qs = pulmonary to systemic blood flow, DLco = diffusing capacity for carbon monoxide. Haemodynamics measured at right heart catheterisation: mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, CO = cardiac output, CI = cardiac index, PVR = pulmonary vascular resistance, PVRi = pulmonary vascular resistance indexed for body surface area, PA = pulmonary arterial

3.5 Discussion

In the current manuscript we describe our experience of patients with PAPVD referred to a pulmonary hypertension referral centre over a 10-year period. To our knowledge this represents the largest, to date, published cohort of patients with PAPVD-associated PH.

Out of 90 patients with PAPVD, 71 (79%) had not been previously identified as having congenital heart disease, despite CT scanning having been performed locally prior to referral in 49 (54%) patients. Furthermore, of the 31 patients with an ASD visible on CT, the diagnosis was newly made by our unit in 25. Jujo *et al* previously studied 8 patients identified with PAPVD at RHC over a 12 year period and found that the diagnosis had been missed on initial reporting of CT scans in 50% of cases (179). Our new data highlight the importance of considering the possibility of APVD +/- ASD in all patients in whom pulmonary hypertension is suspected. It can be difficult to identify APVD and SV-ASD using standard transthoracic echocardiography (180). Many patients undergo CT scanning prior to referral to a pulmonary hypertension specialist centre and as part of a systematic evaluation of the thoracic CT, the course of all 4 pulmonary veins should be assessed (Figure 10).

The majority of patients (67%) had anomalous drainage limited to the right superior pulmonary vein, with 29% involving left-sided veins. Most previous clinical series of patients presenting with symptomatic PAPVD also reported predominantly right-sided PAPVD although 2 recent population-based CT studies observed a left-sided predominance (173, 181). The reason for this discrepancy is not clear. In keeping with previous studies, however, we identified that the majority of patients with PAPVD in our cohort were female (173, 181, 182).

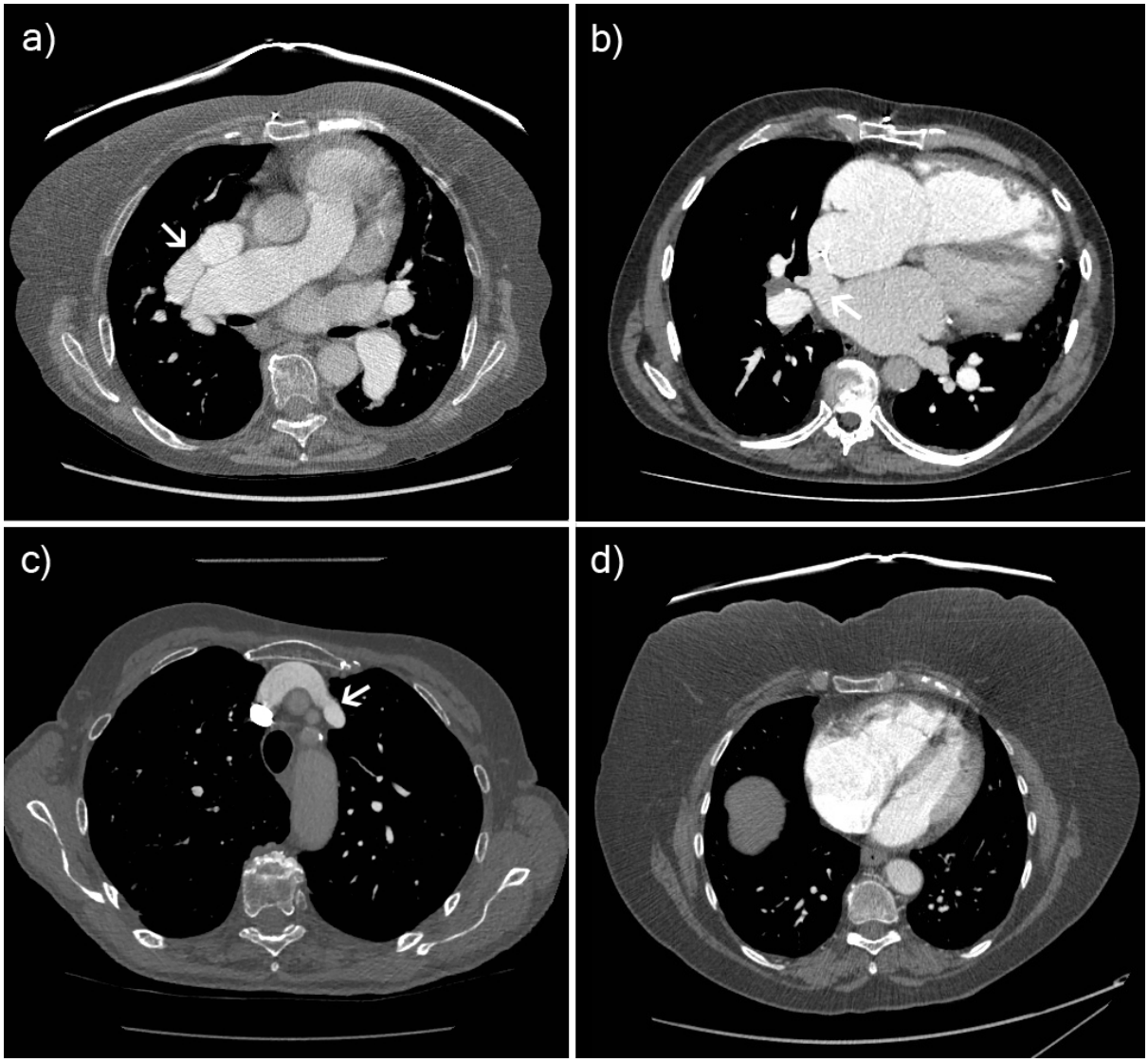

Figure 10: Contrast-enhanced CT scans of variants of PAPVD: a) anomalous drainage of right superior vein into SVC (arrow); b) SV-ASD (arrow); c) anomalous drainage of left superior vein into brachiocephalic vein (arrow); d) enlargement of anteriorly-located right heart chambers in a patient with PAPVD.

Abbreviations: SV-ASD = sinus venosus atrial septal defect; PAPVD = partial anomalous pulmonary venous drainage.

We hypothesised that patients with >1 anomalous vein in the absence of an ASD would have evidence of greater L-R shunt than those with a single abnormal vein. Although there was no difference in terms of RV area on CT, we did observe a greater Qp:Qs and higher DLco %pred in patients with abnormal drainage of multiple lobes. This is consistent with previous observations by Majdalany *et al* who reported 43 patients with isolated PAPVD seen during a 20-year period; the vast majority of patients with RV dilatation who required surgery had >1 abnormal pulmonary vein (183). We similarly hypothesised that the 31 patients with associated ASDs would have larger L-R shunts than those without associated defects and, indeed, in those patients RV and pulmonary artery diameters and cardiac MRI-assessed Qp:Qs were higher. We also hypothesised that this increased Qp:Qs would be reflected in standard non-invasive physiological measurements. DLco %pred was higher in those patients with associated septal defects, in keeping with increased pulmonary capillary blood flow. These observations were contrary to those of Sahay *et al* who did not see any effect of the presence or absence of an associated ASD difference on Qp:Qs in patients identified at a large ACHD centre over a 5-year period (184). The number of patients in that study was, however, relatively small (n=14, 6 of whom had PAH).

Left atrial pressure as assessed by PAWP was elevated in 24 patients. In a normal person, each pulmonary vein drains approximately 25% of the total pulmonary blood flow (185). However, in anomalous pulmonary venous drainage, the shunt flow may be higher since the circulation is preferentially directed to the right side due to lower pressure in the RA and superior vena cava than in the left atrium. This effect becomes more pronounced in conditions that increase left atrial pressure such as systemic hypertension or left heart disease. It is interesting to note that the right-sided chambers were significantly larger and there was a trend towards a larger pulmonary artery in those patients with an elevated PAWP.

In addition to elevated left atrial pressure, other potential causes of PH were present in 29% of patients with PH. In their report of 43 patients with isolated PAPVD, Majdalany *et al* observed emphysema or interstitial lung disease in 6 patients, chronic thromboembolic disease in 4 patients and cirrhosis in 2 patients (183). It is possible that these associated conditions may act as a "second hit" on a pulmonary vasculature already exposed to increased flow leading to the development of PH.

Optimal treatment of patients with PAPVD depends on the anatomical and haemodynamic picture. Our practice is to recommend subsequent referral of all patients with newly diagnosed PAPVD +/- ASD to their regional ACHD centre for an evaluation regarding surgical suitability. The role of PAH therapy in patients with PAH associated with PAPVD +/- ASD is not clear. Although there are several case studies and small case series reporting improvement with PAH therapy in patients with PAPVD and

PAH, no such patients have been studied in randomised controlled trials (174, 186-188). Consideration for PAH therapy should therefore be done on a case-by-case basis taking into account pulmonary haemodynamics and the extent of L-R shunt. In certain circumstances, reassessment of haemodynamics following PAH therapy may alter initial decisions regarding suitability for intervention.

Limitations

This was a retrospective study and hence data for certain investigations, including inferior venocaval saturations enabling invasive Qp:Qs calculation, were not available for all patients. Some haemodynamic data provided should be interpreted with caution: the PA lobe in which the PAWP was measured was not recorded, and the PAWP will be inaccurate if the catheter is wedged in an artery supplying an anomalous lobe. In addition, previous studies have highlighted that cardiac output measured by thermodilution may be inaccurate in patients with left-to-right intra-cardiac shunts, which may affect the data described in patients with PAPVD with associated ASD (189, 190). We have therefore presented data regarding Qp:Qs based on patients who had undergone Qp and Qs measurement at cardiac MRI.

3.6 Conclusions

Undiagnosed PAPVD +/- ASD may be present in patients with suspected PH who are referred to a specialist referral centre. The presence or absence of PAPVD on cross-sectional imaging should therefore be specifically assessed in all patients with suspected PH. Radiological and physiological markers of pulmonary blood flow are higher in patients with an associated SV-ASD in keeping with increased L-R shunt. Although many patients with PAPVD and PH may have other potential causes of PH, a proportion of patients diagnosed with PAH have isolated APVD in the absence of other causative conditions.

4. Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension

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4.1 Abstract

There are limited published data defining survival and treatment response in patients with mild lung disease and/or reduced gas transfer who fulfil diagnostic criteria for idiopathic pulmonary arterial hypertension (IPAH).

Patients diagnosed with IPAH between 2001-19 were identified in the ASPIRE registry. Using pre-specified criteria based on CT imaging and spirometry, patients with a diagnosis of IPAH and no lung disease were termed $IPAH_{no\text{-}LD}$ (n=303), and those with minor-mild emphysema or fibrosis were described as $IPAH_{mild\text{-}LD}$ (n=190).

Survival was significantly better in $IPAH_{no\text{-}LD}$ than in $IPAH_{mild\text{-}LD}$ (1 and 5-year survival 95% and 70% versus 78% and 22% respectively, $p<0.0001$). In the combined group of $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$, independent predictors of higher mortality were increasing age, lower D_{LCO}, lower exercise capacity and a diagnosis of $IPAH_{mild\text{-}LD}$ (p all <0.05). Exercise capacity and quality of life improved (p both <0.0001) following treatment in patients with $IPAH_{no\text{-}LD}$ but not $IPAH_{mild\text{-}LD}$. A proportion of patients with $IPAH_{no\text{-}LD}$ had a D_{LCO} <45%; these patients had poorer survival than patients with D_{LCO} ≥45% although demonstrated improved exercise capacity following treatment.

The presence of even mild parenchymal lung disease in patients who would be classified as IPAH according to current recommendations has a significant adverse effect on outcomes. This phenotype can be identified using lung function testing and clinical CT reports. Patients with IPAH, no lung disease and severely reduced D_{LCO} may represent a further distinct phenotype. These data suggest that RCTs of targeted therapies in patients with these phenotypes are required.

4.2 Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a rare condition (estimated incidence <5/million/year) defined *haemodynamically* as a mean pulmonary arterial pressure (mPAP) >20 mmHg, a left atrial pressure ≤15 mmHg and a pulmonary vascular resistance (PVR) >3 WU (12, 191). It is defined *clinically* as the absence of conditions or risk factors associated with the development of pre-capillary pulmonary hypertension (PH) including connective tissue disease, congenital heart disease, chronic thromboembolic disease and lung disease (43). Several medical therapies have been shown to improve haemodynamics, exercise capacity and clinical events while survival has improved significantly over the last 3 decades (84, 192, 193). Chronic lung disease associated pulmonary hypertension (CLD-PH) is common; 90% of patients with severe chronic obstructive pulmonary disease (COPD) have a mPAP >20 mmHg (194). Significant pulmonary hypertension in association with lung disease is less common with ≤5% of COPD patients having a mPAP ≥35 mmHg (97).

Mild lung disease may be present in patients with severe pre-capillary haemodynamics. This can create diagnostic uncertainty as to whether a patient has group 1 (pulmonary arterial hypertension; PAH) or group 3 (CLD-PH) disease. The recent 6th World Symposium on Pulmonary Hypertension (WSPH) suggested that patients with co-existing lung disease be diagnosed with PAH when PH is moderate-severe, when only modest spirometric or parenchymal abnormalities are present and when diffusion capacity (D_{LCO}) is low with respect to obstructive or restrictive lung function (194).

There are few data defining survival and treatment response in patients with mild lung disease who fulfil the diagnostic criteria for IPAH suggested by the 6th WSPH. We hypothesised that even mild lung disease and/or low gas transfer have a negative effect on outcomes in patients with a diagnosis of IPAH. We therefore performed a study of characteristics, survival and response to therapy of patients who had been assigned a diagnosis of IPAH at a large PH referral centre over an 18-year period.

4.3 Methods

Patients who had been assigned a diagnosis of IPAH or heritable PAH or CLD-PH between February 2001 and January 2019 at our centre were identified from the ASPIRE registry, a database consisting of consecutive patients referred to the Sheffield Pulmonary Vascular Disease Unit who undergo multi-modality assessment and multi-disciplinary team discussion, as previously described (94). Radiology images and reports, lung function tests, pulmonary haemodynamics and clinical correspondence were retrieved, blinded to outcomes. CT images had been reported at the time of diagnosis by experienced pulmonary vascular radiologists, blinded to haemodynamics and spirometry, using a qualitative assessment of the extent of parenchymal lung disease: none, minor, mild, moderate or severe. In the

absence of moderate to severely abnormal spirometry (defined as FEV_1 <60% and/or FVC <70%), patients with a diagnosis of IPAH or heritable PAH who had no parenchymal lung disease were termed $IPAH_{no\text{-}LD}$ while those who had minor or mild emphysema or fibrosis on their original CT report were termed $IPAH_{mild\text{-}LD.}$ Patients with moderate to severely abnormal spirometry and/or those with moderate or severe parenchymal lung disease were defined as CLD-PH. Patients with PH caused by respiratory disease other than COPD, emphysema or interstitial lung disease (ILD) were excluded. Patients with ≥2 radiological features of possible pulmonary veno-occlusive disease (PVOD; centrilobular ground glass opacities, mediastinal lymphadenopathy and interlobular septal lines) were also excluded (195). Smoking status and history was retrieved from clinical notes.

Quality of life was assessed by emPHasis-10 score (196); scored out of 50, lower score represents lower symptom burden.

Mortality Data

Mortality data were obtained from systems linked to the NHS Personal Demographics Service (PDS), which is updated when a death is registered in the UK. Patients who emigrated (n=3) were excluded, as were patients without a record on the PDS (n=2). Patients undergoing lung transplantation were censored at the time of surgery, and mortality data were collected using a census date of 31st May 2019.

Follow-up

Two follow-up time points were used to assess treatment response: first follow-up beyond 90 days of diagnosis and first follow-up between 9 and 15 months in patients receiving oral combination therapy within 6 months of diagnosis. The latter time point was used to enable comparison between patients who had received a similar therapeutic approach.

Statistics

Statistical analysis was performed using SPSS v25 and GraphPad Prism v8. Unless otherwise specified, continuous data were displayed as mean ±standard deviation (compared using paired/unpaired T-tests), or median (first quartile, third quartile) for non-parametric data (compared using Wilcoxon signed-rank/Mann-Whitney U-tests). Frequencies were compared using the χ^2 test. Multivariate Cox regression was performed in a forward direction on parameters with a *p* value <0.2 at univariate

analysis. To allow comparison at univariate and multivariate analysis, continuous variables were scaled to the mean. For other statistical tests, a *p* value of <0.05 was considered significant. Kaplan-Meier survival curves were compared using the log-rank test, truncated at 5 years. Where appropriate, 95% confidence intervals were derived for median values using a bootstrap resampling technique.

Ethics

Ethical approval was granted by Sheffield Teaching Hospitals NHS Foundation Trust (STH14169) and approved by the National Research Ethics Service (16/YH/0352).

4.4 Results

Of 5643 patients diagnosed with all forms of PH, 493 incident patients were identified who had a diagnosis of either idiopathic or heritable PAH (hereafter grouped as IPAH, who formed the main study population),

Figure 11. Following reassessment of patients assigned a diagnosis of IPAH, 303 had no evidence of parenchymal lung disease ($IPAH_{no\text{-}LD}$) while 190 had minor or mild parenchymal lung disease ($IPAH_{mild\text{-}LD}$). Baseline right heart catheterisation data were available in 98%, spirometry in 97% and D_{LCO} in 83% of patients with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$.

Comparison of $IPAH_{no\text{-}LD}$ vs $IPAH_{mild\text{-}LD}$

Patients with $IPAH_{no\text{-}LD}$ were younger (mean age 53 vs 70 years; p<0.0001), had a female predominance (73% vs 47%; p<0.0001), a higher mean mPAP and mixed venous oxygen saturations (mPAP 55mmHg vs 50mmHg, SvO_2 60% vs 62%; p both <0.05) and were less likely to have a smoking history than patients with $IPAH_{mild\text{-}LD}$ (p<0.0001, Table 5). Spirometric volumes were well preserved in patients with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$. Patients with $IPAH_{no\text{-}LD}$ had significantly better survival than patients who had $IPAH_{mild\text{-}LD}$ (1 and 5-year survival 95% and 70% vs 78% and 22%; p<0.0001, Figure 12). When patients with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$ were analysed together in a multivariate model, independent predictors of higher mortality were increasing age, lower D_{LCO} %predicted, lower ISWD and a diagnosis of $IPAH_{mild\text{-}LD}$ (Table 6). In view of the different forms of parenchymal lung disease encompassed by $IPAH_{mild\text{-}LD}$, this multivariate model was reanalysed using data for the emphysema or interstitial lung disease subtypes separately. Increasing age, lower ISWD and a diagnosis of $IPAH_{mild\text{-}LD}$ remained as independent predictors of mortality. There was no significant difference in survival between patients with $IPAH_{mild\text{-}LD}$ who had emphysema or ILD (Figure 13). Baseline demographics and haemodynamics

of these groups were also very similar (Table 7). Lung function data for subtypes of $IPAH_{mild\text{-}LD}$ are also shown in Table 7.

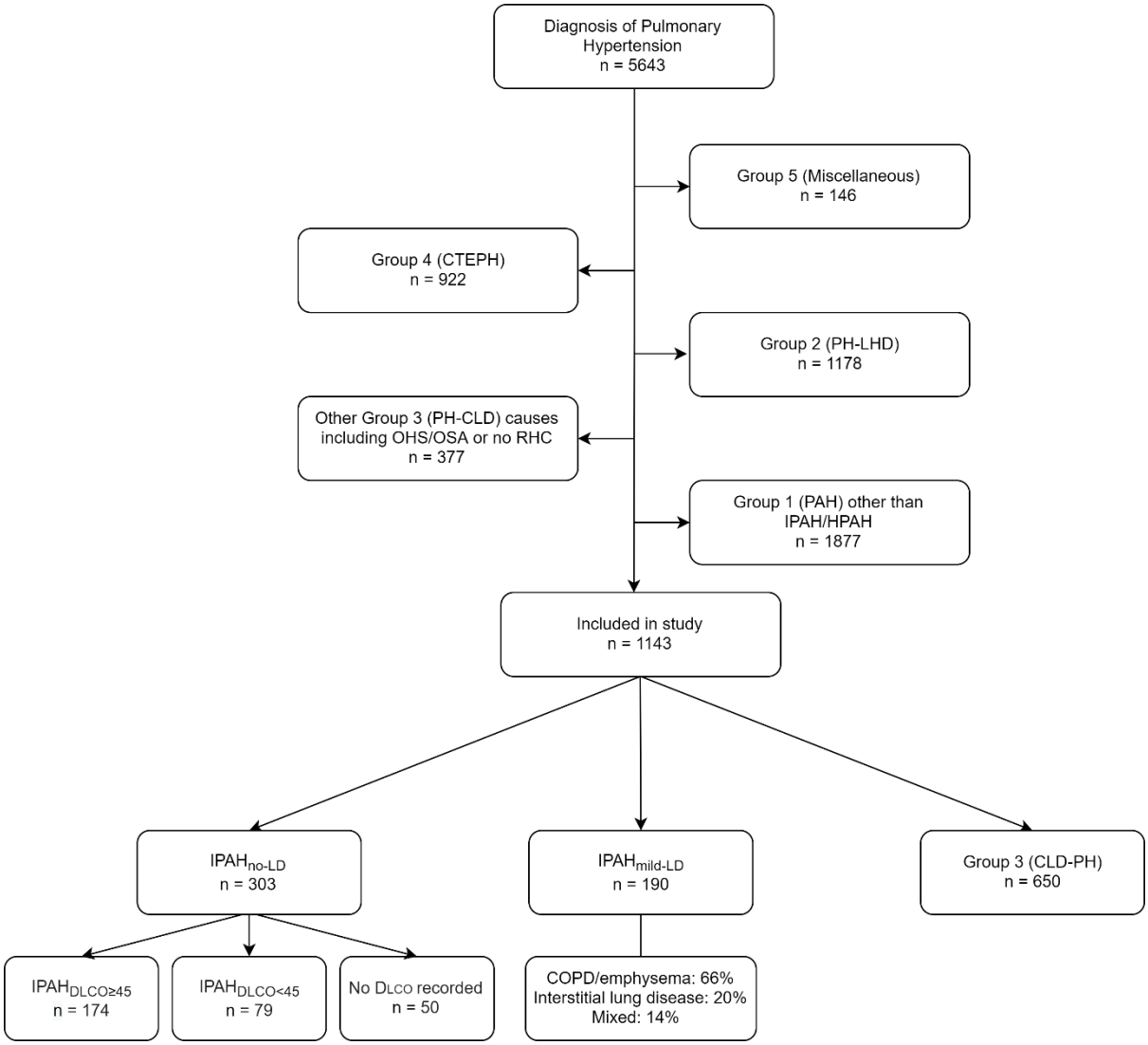

Figure 11: Flow chart demonstrating selection of patients for participation in study

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension, PH-LHD = pulmonary hypertension due to left heart disease, OHS = obesity hypoventilation syndrome, OSA = obstructive sleep apnoea, PAH = pulmonary arterial hypertension, IPAH = idiopathic pulmonary arterial hypertension, HPAH = heritable pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{DLCO\geq45}$ = IPAH with no lung disease with D_{LCO} ≥45% predicted, $IPAH_{DLCO<45}$ = IPAH with no lung disease with D_{LCO} <45% predicted, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease, COPD = chronic obstructive pulmonary disease.

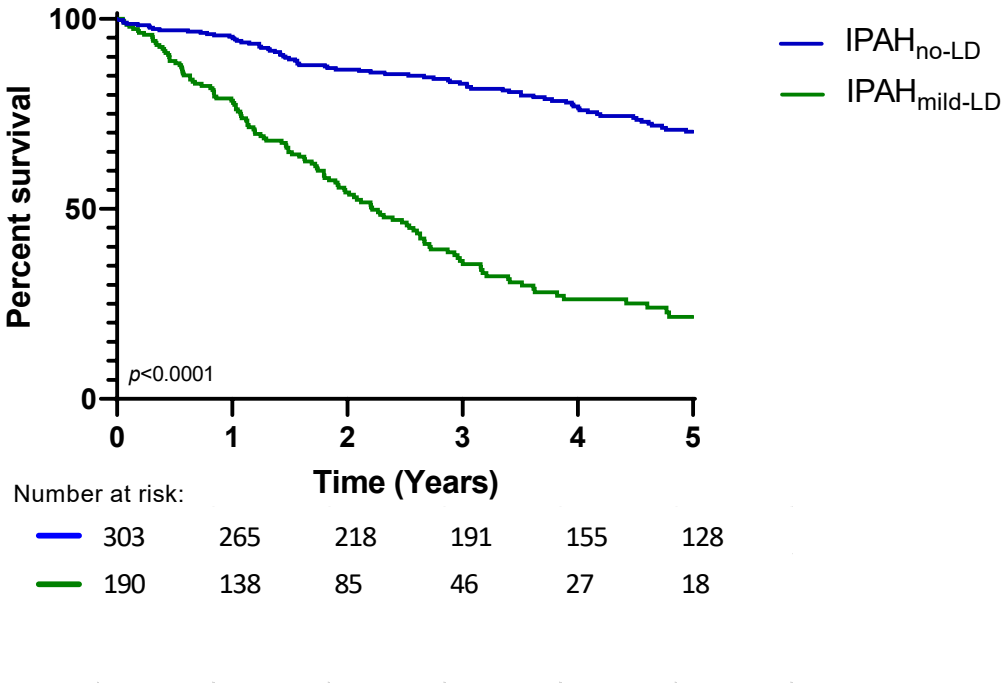

Figure 12: Survival from diagnosis in $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease

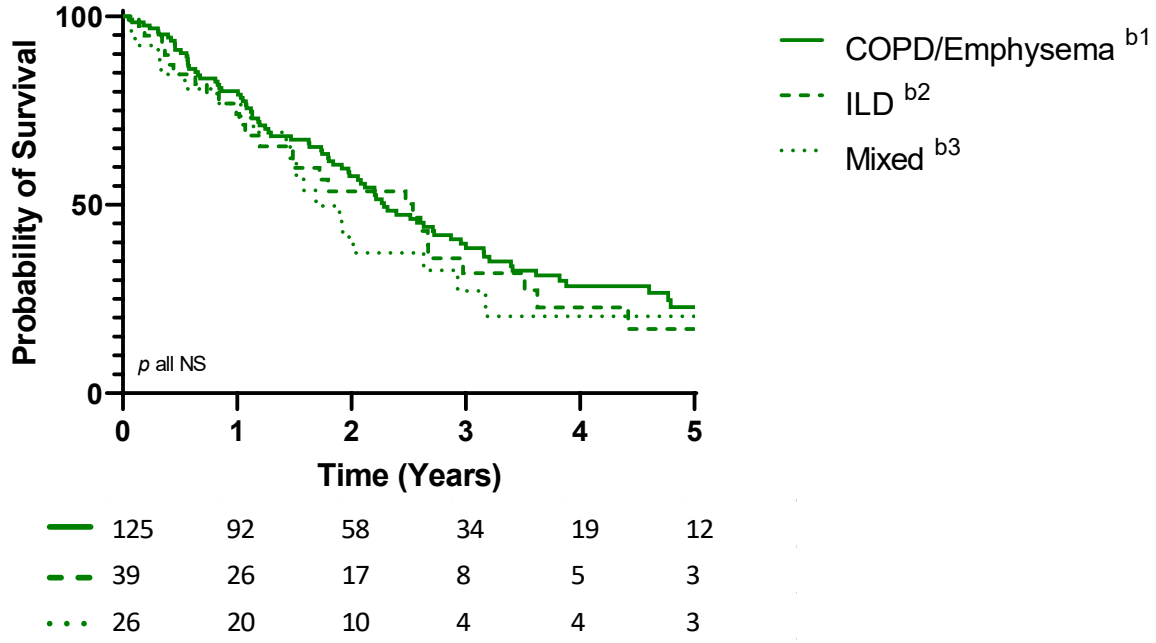

Figure 13: Survival by subtype of lung disease in IPAH$_{mild\text{-}LD}$

Abbreviations: COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease

Table 5: Baseline demographics and maximal treatment data

	$IPAH_{no\text{-}LD}$	**$IPAH_{mild\text{-}LD}$**	***p* value**
Number	303	190	
Female (%)	73	47	<0.0001
Age (years)	53 ±17	70 ±10	<0.0001
WHO FC I/II/III/IV (%)	0/21/60/19	0/9/56/35	
BMI (kg/m^2)	29 ±6	28 ±6	0.15
mRAP (mmHg)	11 ±6	11 ±5	0.39
mPAP (mmHg)	55 ±13	50 ±9	<0.0001
PAWP (mmHg)	10 ±3	11 ±3	0.10
PVR (WU)	11.9 ±5.8	11.1 ±4.5	0.10
SvO_2 (%)	62 ±9	59 ±9	0.02
Cardiac Output (L/min)	4.3 ±1.6	4.0 ±1.4	0.04
Cardiac Index ($L/min/m^2$)	2.3 ±0.8	2.2 ±0.7	0.07
FEV1 %	89 ±15	89 ±17	0.64
FVC %	100 ±17	103 ±18	<0.05
FEV1/FVC	75 ±9	68 ±8	<0.0001
D_{LCO} %pred	56 ±20	30 ±13	<0.0001
ISWD (m)	210 (80, 360)	80 (40, 180)	<0.0001
% smokers	40	82	<0.0001
Pack-years in smokers	25 ±17	32 ±18	0.03
Maximal Treatment (%)*			
None	1	1	
CCB	5	1	
Oral mono	19	34	
Combo oral	44	50	
Prostanoid +/- oral	31	14	

*This refers to the maximal treatment received during the study. Data are presented as mean ±SD or median (Q1, Q3). Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease, WHO FC = World Health Organisation functional class, BMI = body mass index, mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance, SvO_2 = mixed venous oxygen saturations, D_{LCO} %pred= diffusing capacity for carbon monoxide percent-predicted, ISWD = incremental shuttle walking test distance, CCB = calcium-channel blockers.

Table 6: Univariate and Multivariate Cox regression analysis of prognostic factors in patients with $IPAH_{no\text{-}LD}$ or $IPAH_{mild\text{-}LD}$

	Univariate		**Multivariate**	
	Scaled HR	**p-value**	**Scaled HR**	**p-value**
$IPAH_{mild\text{-}LD}$ (ref. $IPAH_{no\text{-}LD}$)	4.287	<0.0001	2.168	<0.0001
Age (yrs)	2.320	<0.0001	1.432	0.014
Gender (ref. female)	1.549	0.001		
Smoking history (ref. none)	2.373	<0.0001		
WHO FC III&IV (ref. I&II)	3.246	<0.0001		
FEV_1 %pred	0.995	0.945		
FVC %pred	1.072	0.328		
FEV_1/FVC	0.767	<0.0001		
D_{LCO} %pred	0.340	<0.0001	0.739	0.039
mRAP (mmHg)	1.239	<0.0005		
PVR (WU)	0.999	0.986		
SvO_2 (%)	0.740	<0.0001		
Cardiac Index (L/min/m^2)	0.788	0.003		
ISWD (m)	0.434	<0.0001	0.559	<0.0001

For continuous variables, hazard ratios are scaled to the mean.

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease, ref = reference, WHO FC = World Health Organisation functional class, D_{LCO} %pred= diffusing capacity for carbon monoxide percent-predicted, mRAP = mean right atrial pressure, PVR = pulmonary vascular resistance, SvO_2 = mixed venous oxygen saturations, ISWD = incremental shuttle walking test distance, HR = Hazard Ratio

Table 7: Baseline demographics in patients with subtypes of $IPAH_{mild\text{-}LD}$ compared with $IPAH_{no\text{-}LD}$

	$IPAH_{no\text{-}LD}$	**$IPAH_{mild\text{-}LD}$ emphysema**	**$IPAH_{mild\text{-}LD}$ fibrosis**	**$IPAH_{mild\text{-}LD}$ Mixed**
Number	303	125	39	26
Female (%)	73	52	39	39
Age	53 ±17 ¶, *, #	70 ±9 z	71 ±10 z	69 ±11 z
WHO FC I/II/III/IV (%)	0/21/60/19	0/9/60/31	0/13/49/38	0/4/50/46
BMI (kg/m^2)	29 ±6	28 ±6	29 ±5	28 ±5
mRAP (mmHg)	11 ±6	11 ±5	11 ±5	10 ±5
mPAP (mmHg)	55 ±13 ¶, *, #	51 ±9 z	48 ±10 z	51 ±8 z
PAWP (mmHg)	10 ±3 ¶	11 ±3 z	10 ±4	10 ±3
PVR (WU)	11.9 ±5.8	10.9 ±4.4	11.1 ±4.5	11.8 ±5.2
SvO_2 (%)	62 ±9 #	60 ±8	60 ±10	57 ±9 z
Cardiac Output (L/min)	4.3 ±1.6	4.1 ±1.5	3.8 ±1.2	3.7 ±1.1
Cardiac Index ($L/min/m^2$)	2.3 ±0.8	2.2 ±0.7	2.1 ±0.6	2.0 ±0.6
FEV1 %	89 ±15	88 ±16	88 ±17	91 ±20
FVC %	100 ±17 ¶	105 ±17 z, *	97±19 ¶	100 ±19
FEV1/FVC	75 ±9 ¶, *, #	66 ±8 z,*	72 ±7 z, ¶	71 ±10 z
D_{LCO} %pred	56 ±20 ¶, *, #	31 ±14 z, #	31±13 z, #	25 ±7 ¶, *, z
ISWD (m)	210 (80, 360) ¶, *, #	90 (40, 190) z	60 (20, 140) z	90 (30, 120) z

Data are presented as mean ±SD or median (Q1, Q3). z p<0.05 in comparison to $IPAH_{no\text{-}LD}$, ¶ p<0.05 in comparison to mild LD emphysema, *p<0.05 in comparison to mild LD fibrosis, # p<0.05 in comparison to mild LD mixed

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease, WHO FC = World Health Organisation functional class, BMI = body mass index, mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance, SvO_2 = mixed venous oxygen saturations, D_{LCO} %pred= diffusing capacity for carbon monoxide percent-predicted, ISWD = incremental shuttle walking test distance.

Effect of D_{LCO} on survival in $IPAH_{no\text{-}LD}$

A bimodal distribution of D_{LCO} %predicted (modes 30, 65) was observed in patients with $IPAH_{no\text{-}LD}$ with an optimal cut-point of 45% (Figure 16). Patients with $IPAH_{no\text{-}LD}$ who had a D_{LCO} <45%predicted ($IPAH_{DLCO<45}$) were older (mean 65 vs 48 years), had a lower mPAP (51 vs 56 mmHg) but also a lower SvO_2 (60% vs 63%) than patients with D_{LCO} ≥45%predicted ($IPAH_{DLCO\geq45}$); *p* all <0.05. Detailed demographics are shown in Table 8. Those with $IPAH_{DLCO<45}$ were more likely to have a history of smoking (52% v 36%, $p<0.05$). There was no significant difference in lung volumes (FEV_1 88% vs 91%, FVC 100% vs 100%, *p* both >0.05) but FEV_1/FVC ratio was lower (71% vs 76%; $p<0.0001$) in patients with $IPAH_{DLCO<45}$. One and five-year survival was significantly lower in patients with $IPAH_{DLCO<45}$ (86% and 45% vs 99% and 84%; $p<0.0001$, Figure 15); this survival difference persisted when adjusted for age.

Response to treatment

Ninety-nine percent of patients with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$ received PAH therapy; treatment response data are shown in Table 10 and Figure 14. Baseline ISWD was significantly higher in $IPAH_{no\text{-}LD}$ than $IPAH_{mild\text{-}LD}$: median 210m vs 80m; $p<0.0001$. There was no significant difference in time to follow-up between patients with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$. At both first follow-up, and at one-year assessment in patients who received combination oral therapy within 6 months of diagnosis, patients with $IPAH_{no\text{-}LD}$ demonstrated significant improvement with respect to ISWD and quality of life score ($p<0.0001$) whereas patients with $IPAH_{mild\text{-}LD}$ did not. In patients receiving oral combination therapy within 6 months of diagnosis, survival was significantly better in patients with $IPAH_{no\text{-}LD}$ compared to patients with $IPAH_{mild\text{-}LD}$ (1 and 5-year survival 98% and 74% vs 71% and 13%; $p<0.0001$, Figure 17). Patients with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$ who received oral combination therapy within 6 months of diagnosis and had one-year follow-up data available had more severe haemodynamics than those who did not; haemodynamic and treatment data for all patients who had follow-up assessments available are displayed in Table 9.

In the $IPAH_{no\text{-}LD}$ group, significant change (Δ) in ISWD was seen in patients with $IPAH_{DLCO<45}$ (median Δ+20m) and $IPAH_{DLCO\geq45}$ (Δ+50m) who received treatment; p both <0.05. Baseline emPHasis-10 scores were significantly higher in patients with $IPAH_{DLCO<45}$ than in patients with $IPAH_{DLCO\geq45}$ (median 38 vs 27; $p<0.01$). Median change in emPHasis-10 at follow-up was not significant in patients with $IPAH_{DLCO<45}$ (ΔemPHasis-10 -4; $p=0.08$) but was significant in patients with $IPAH_{DLCO\geq45}$ (ΔemPHasis-10 -4; $p<0.05$).

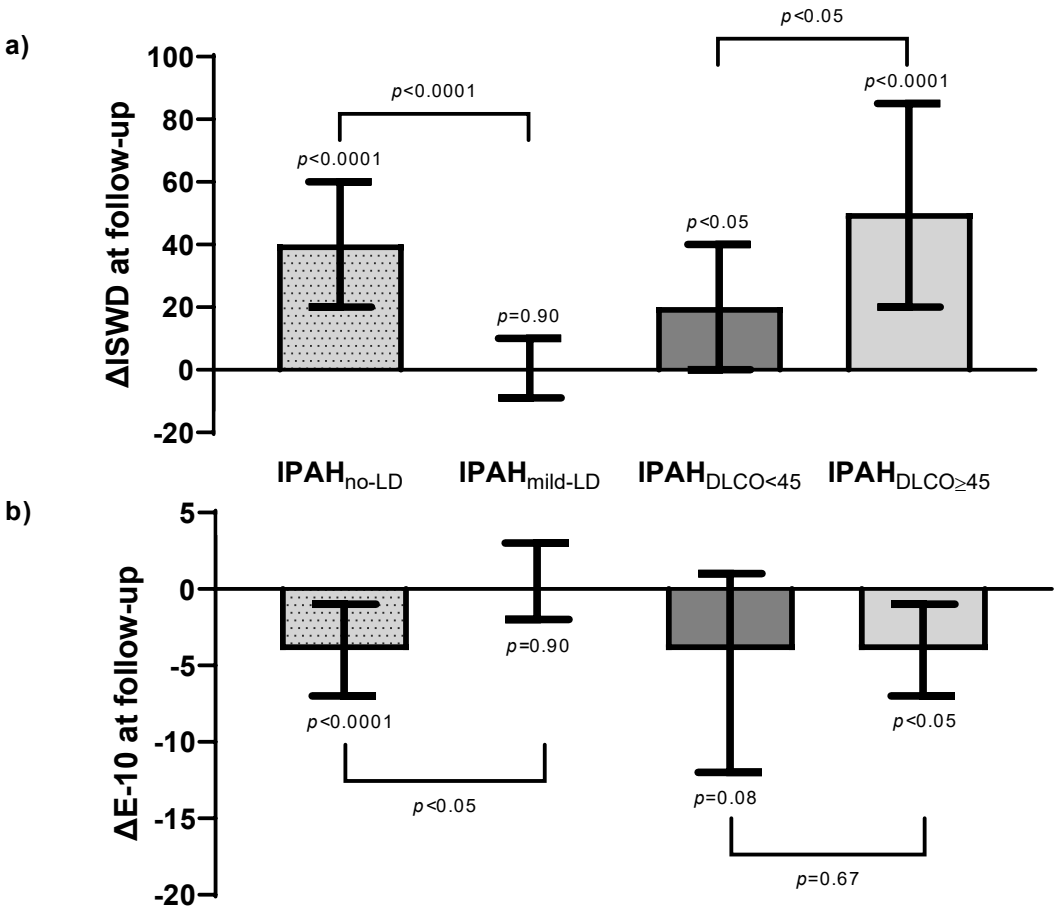

Figure 14: Change at first follow-up beyond 90 days in a) ISWD; b) emPHasis-10

All values displayed as median with 95% confidence intervals

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease, $IPAH_{DLCO<45}$ = $IPAH_{no\text{-}LD}$ with D_{LCO} <45% predicted, $IPAH_{DLCO\geq45}$ = $IPAH_{no\text{-}LD}$ with D_{LCO} ≥45% predicted, ISWD = incremental shuttle walking test distance, E-10 = emPHasis-10 quality of life score

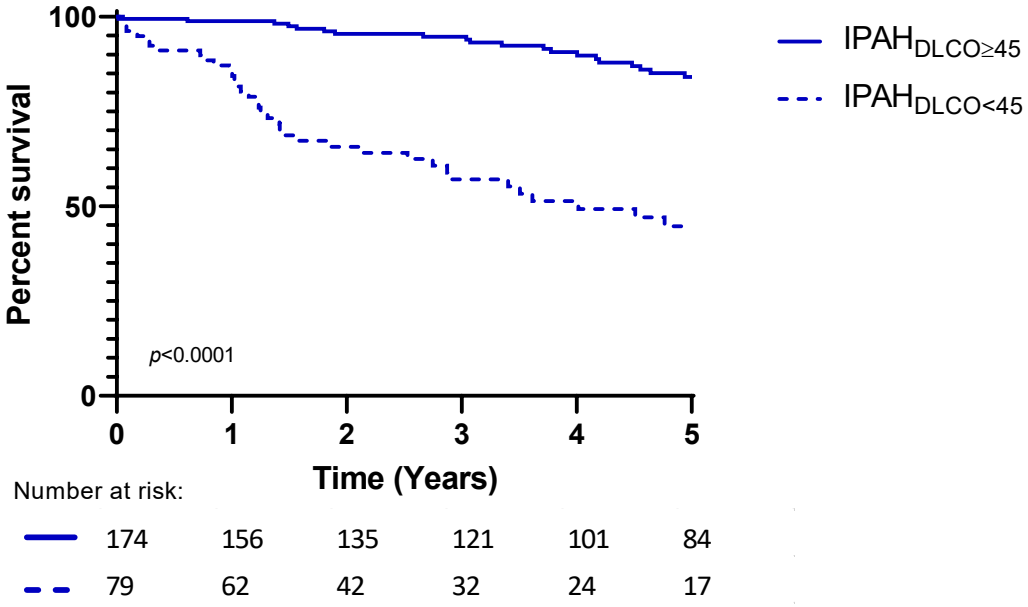

Figure 15: Survival in IPAH patients with no lung disease ($IPAH_{no\text{-}LD}$) stratified by D_{LCO} <45% predicted ($IPAH_{DLCO<45}$) versus D_{LCO} ≥45% predicted ($IPAH_{DLCO\geq45}$)

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, D_{LCO} = diffusion capacity for carbon monoxide, $IPAH_{DLCO<45}$ = $IPAH_{no\text{-}LD}$ with D_{LCO} <45% predicted, $IPAH_{DLCO\geq45}$ = $IPAH_{no\text{-}LD}$ with D_{LCO} ≥45% predicted.

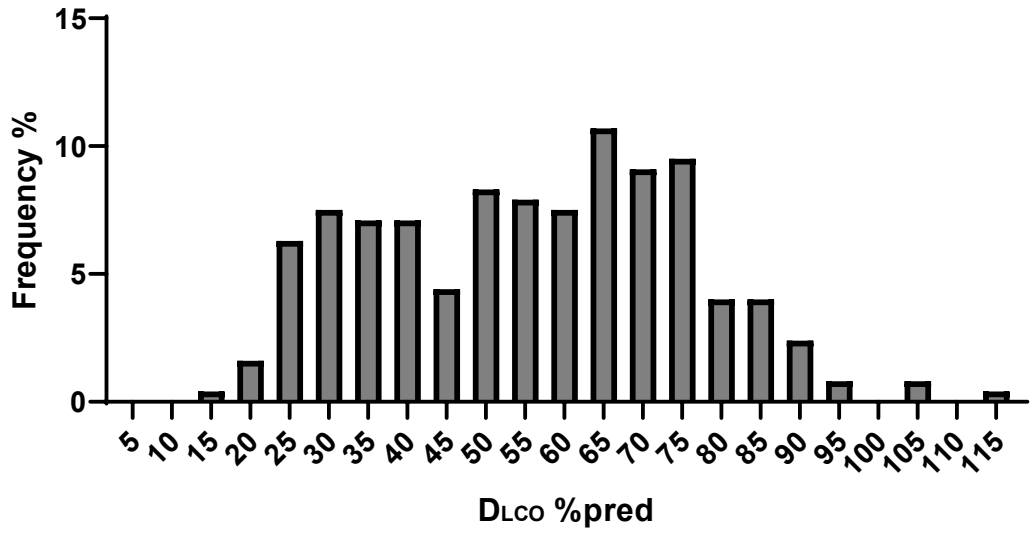

Figure 16: Distribution of D_{LCO} %predicted in patients with $IPAH_{no\text{-}LD}$

Abbreviations: D_{LCO} %pred = percent-predicted diffusing capacity for carbon monoxide, $IPAH_{no\text{-}LD}$ = idiopathic pulmonary arterial hypertension with no lung disease.

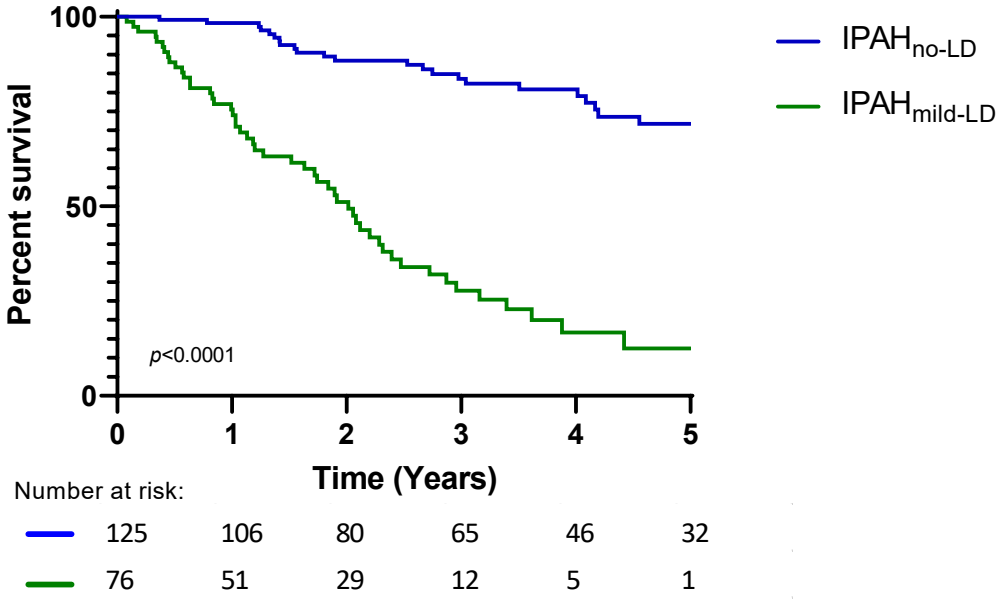

Figure 17: Survival in patients with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$ treated with oral combination therapy within 6 months of diagnosis

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease.

Table 8: Demographics for subgroups of IPAH

	$IPAH_{no\text{-}LD}$	**$IPAH_{mild\text{-}LD}$**	**$IPAH_{DLCO<45}$**	**$IPAH_{DLCO\geq45}$**
Number	303	190	79	174
Female (%)	73	47	66	77
Age	53 ±17	70 ±10	65 ±12	48 ±16
WHO FC I/II/III/IV (%)	0/21/60/19	0/9/56/35	0/12/57/31	0/24/65/11
mRAP (mmHg)	11 ±6	11 ±5	11 ±7	11 ±6
mPAP (mmHg)	55 ±13	50 ±9	51 ±10	56 ±14
PAWP (mmHg)	10 ±3	11 ±3	10 ±3	10 ±3
PVR (WU)	11.9 ±5.8	11.1 ±4.5	11.4 ±5.3	12.3 ±6.1
SvO_2 (%)	62 ±9	59 ±9	60 ±9	63 ±9
Cardiac Output (L/min)	4.3 ±1.6	4.0 ±1.4	4.2 ±1.6	4.2 ±1.4
Cardiac Index (L/min/m^2)	2.3 ±0.8	2.2 ±0.7	2.3 ±0.9	2.3 ±0.8
FEV1 %	89 ±15	89 ±17	88 ±19	91 ±13
FVC %	100 ±17	103 ±18	100 ±20	100 ±15
FEV1/FVC	75 ±9	68 ±8	71 ±10	76 ±7
DLCO %pred	56 ±20	30 ±13	32 ±7	67 ±13
ISWD (m)	210 (80, 360)	80 (40, 180)	80 (30, 210)	260 (130, 430)
emPHasis-10 score	32 (20,40)	32 (26, 41)	38 (33, 44)	28 (20, 35)
One-year mortality (%)	4.9	21.5	14.2	1.2

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease, $IPAH_{DLCO<45}$ = IPAH with D_{LCO} <45%, $IPAH_{DLCO\geq45}$ = IPAH with D_{LCO} ≥45%, WHO FC = World Health Organisation functional class, BMI = body mass index, mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance, SvO_2 = mixed venous oxygen saturations, D_{LCO} %pred = diffusing capacity for carbon monoxide percent predicted, ISWD = incremental shuttle walking test distance.

Table 9: Demographics in patients with follow-up data available

	IPAH$_{no-LD}$	**IPAH$_{mild-LD}$**	**IPAH$_{DLCO<45}$**	**IPAH$_{DLCO≥45}$**	**IPAH$_{no-LD}$ ***	**IPAH$_{mild-LD}$ ***
Number	215	124	47	139	79	32
Female (%)	73 ¶	47 ¶	66	77	85 #	31 #
Age	51 ±17 ¶	70 ±10 ¶	65 ±13 ¥	48 ±16 ¥	51 ±17 #	69 ±9 #
WHO FC I/II/III/IV (%)	0/23/60/17	0/10/64/26	0/11/66/23	0/26/63/11	0/16/70/14	0/3/63/34
BMI (kg/m^2)	29 ±6	28 ±6	29 ±6	29 ±6	30 ±7	30 ±6
mRAP (mmHg)	11 ±6	11 ±5	11 ±6	11 ±6	13 ±6	12 ±4
mPAP (mmHg)	56 ±12 ¶	50 ±9 ¶	52 ±9 ¥	56 ±13 ¥	60 ±13 #	55 ±10 #
PAWP (mmHg)	10 ±3	11 ±3	10 ±3	10 ±3	10 ±4 #	12 ±3 #
PVR (WU)	12.0 ±5.7 ¶	10.7 ±4.4 ¶	11.6 ±4.8	12.4 ±5.9	14.4 ±5.0 #	11.6 ±3.8 #
SvO_2 (%)	62 ±9 ¶	59 ±9 ¶	60 ±10 ¥	63 ±9 ¥	60 ±9	58 ±6
Cardiac Output (L/min)	4.3 ±1.5	4.0 ±1.4	4.1 ±1.5	4.1 ±1.3	3.8 ±1.2	3.9 ±1.3
Cardiac Index (L/min/m^2)	2.3 ±0.8	2.2 ±0.7	2.2 ±0.7	2.3 ±0.7	2.1 ±0.6	2.0 ±0.6
FEV1 %	90 ±15	88 ±17	88 ±20	91 ±13	88 ±14	91 ±17
FVC %	101 ±17	103 ±17	102 ±22	101 ±15	101 ±18	107 ±16
FEV1/FVC	75 ±8 ¶	67 ±9 ¶	70 ±10 ¥	76 ±7 ¥	74 ±9 #	68 ±10 #
D_{LCO} %pred	58 ±19 ¶	31 ±14 ¶	32 ±7 ¥	67 ±13 ¥	57 ±18 #	33 ±14 #
ISWD (m)	210 (80, 360) ¶	90 (40, 180) ¶	70 (20, 200) ¥	265 (130, 430) ¥	210 (90, 340) #	130 (50, 210) #
Treatment (%)						
None	1	0	0	1	0	0
CCB	6	1	0	9	0	0
Oral mono	13	34	17	11	0	0
Combo oral	48	45	53	47	66	69
Prostanoid +/- oral	32	20	30	32	34	31

* denotes subgroups of patients receiving combination oral therapy within 6 months of diagnosis

Data are presented as mean ±SD or median (Q1, Q3). ¶ $p<0.05$ between $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$, ¥ $p<0.05$ between $IPAH_{DLCO<45}$ and $IPAH_{DLCO\geq45}$, # $p<0.05$ between $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$ (patients receiving oral combination therapy within 6 months of diagnosis)

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease, $IPAH_{DLCO<45}$ = IPAH with D_{LCO} <45%, $IPAH_{DLCO\geq45}$ = IPAH with D_{LCO} ≥45%, WHO FC = World Health Organisation functional class, BMI = body mass index, mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance, SvO_2 = mixed venous oxygen saturations, D_{LCO} %pred = diffusing capacity for carbon monoxide percent predicted , ISWD = incremental shuttle walking test distance.

Table 10. Baseline and follow-up incremental shuttle walking test distance and emPHasis-10 score

	N	$IPAH_{no\text{-}LD}$	N	$IPAH_{mild\text{-}LD}$	N	$IPAH_{DLCO<45}$	N	$IPAH_{DLCO\geq45}$
Baseline and first follow-up beyond 90 days								
Baseline ISWD (m)	279	210 (80, 360)	159	80 (40, 180) ****	71	80 (30, 210)	170	260 (130, 430) ++++
ΔISWD (m)	215	40 (-10, 120)	124	0 (-32, 30) ****	47	20 (-13, 70)	139	50 (-10, 160) +
ΔISWD *p*-value		<0.0001		0.90		<0.05		<0.0001
Baseline E-10	84	32 (20, 40)	83	32 (26, 41)	25	38 (33, 44)	55	27 (0, 35) ++
ΔE-10	64	-4 (-12, +3)	65	0 (-5, +8) *	19	-4 (-13, +2)	43	-4 (-11, +3)
ΔE-10 *p*-value		0.005		0.57		0.08		0.03
Baseline and 1-year follow-up: Patients treated with combination oral treatment within 6 months of diagnosis								
Baseline ISWD (m)	125	200 (80, 340)	76	60 (20, 140) ****				
ΔISWD (m)	79	40 (-10, 140)	32	-20 (-50, 50) **				
ΔISWD *p*-value		<0.0001		0.83				
Baseline E-10	57	34 (22, 42)	41	35 (28, 41)				
ΔE-10	27	-4 (-18, +5)	17	-4 (-11, +3)				
ΔE-10 *p*-value		0.03		0.19				

* $p<0.05$; ** $p<0.01$; *** $p<0.001$; **** $p<0.0001$ compared to $IPAH_{no\text{-}LD}$

+ $p<0.05$; ++ $p<0.01$; +++ $p<0.001$; ++++ $p<0.0001$ compared to $IPAH_{DLCO<45}$

Data are presented as median (Q1, Q3). Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, $IPAH_{no\text{-}LD}$ = IPAH with no lung disease, $IPAH_{mild\text{-}LD}$ = IPAH with mild lung disease, $IPAH_{DLCO<45}$ = $IPAH_{no\text{-}LD}$ with D_{LCO} <45% predicted, $IPAH_{DLCO\geq45}$ = $IPAH_{no\text{-}LD}$ with D_{LCO} ≥45% predicted, ISWD = incremental shuttle walking test distance, E-10 = emPHasis-10 quality of life score.

4.5 Discussion

In the current study we have reassessed a large number of patients who had been assigned a diagnosis of IPAH at a large PH referral centre. By using radiology reports and lung function from the time of diagnosis we have identified phenotypes of IPAH with different characteristics, response to therapy and survival. Specifically, we have demonstrated that the presence of even mild parenchymal lung disease in patients who have been diagnosed with IPAH ($IPAH_{mild\text{-}LD}$) is associated with a distinct clinical picture (well-preserved spirometry, low D_{LCO} %pred and severe PH) and has a large negative effect on outcomes. We have also observed that a proportion of patients with IPAH with no parenchymal lung disease and unremarkable spirometry have a low D_{LCO}. Differentiation of IPAH from CLD-PH represents a continual diagnostic challenge to all involved in the care of patients with PH. Mild PH in the context of severe lung disease (assessed radiologically and/or spirometrically) is common, and easily ascribed to group 3 (CLD-PH). Likewise, most would agree that patients with severe pulmonary haemodynamics and severe lung disease, where the severity of PH is proportionate to the degree of lung disease, also have group 3 disease. The presence of more modest lung disease in patients who fulfil traditional criteria for IPAH presents greater diagnostic and therapeutic challenges.

Survival and response to therapy in $IPAH_{mild\text{-}LD}$

In the current study, survival in patients with $IPAH_{mild\text{-}LD}$ was significantly worse than in $IPAH_{no\text{-}LD}$. In addition, although patients with $IPAH_{no\text{-}LD}$ experienced significant improvements in walk distance and emPHasis-10 score following initiation of PAH therapies, this same improvement was not observed in patients with $IPAH_{mild\text{-}LD}$. Some retrospective studies of patients with mild-to-moderate lung disease and severe PH have reported improved haemodynamics and exercise capacity following commencement of PAH therapies (100-102). Conversely, Brewis *et al* failed to demonstrate improvement in 6-minute walk distance (6MWD) or WHO functional class in 118 patients with severe PH and varying degrees of lung disease following PAH therapy, while we have previously reported treatment response to pulmonary vascular therapy in only 19% of patients with severe CLD-PH (103, 197). Prospective randomised controlled studies (RCTs) of PAH therapies in patients with CLD-PH due to COPD/emphysema have suffered from methodological weaknesses (104, 105) or recruited patients with mild PH (106, 107), although Vitulo *et al* recently performed a RCT in 31 patients with severe CLD-PH due to COPD and demonstrated significant improvements in pulmonary haemodynamics but no improvement in 6MWD (108).

The 6th WSPH task force on CLD-PH recommended that in patients with co-existing lung disease, PAH should be diagnosed when PH is moderate-severe, when only modest spirometric (i.e. FEV_1>60% and

FVC>70%) or parenchymal abnormalities are present and when D_{LCO} is low with respect to obstructive or restrictive lung function (194). Using these criteria, patients in our $IPAH_{mild\text{-}LD}$ group would keep their original diagnosis of IPAH. Our observations regarding the effect that mild parenchymal lung disease has on response to therapy and survival suggests that $IPAH_{mild\text{-}LD}$ is a distinct phenotype and that further prospective studies to assess treatment response in these patients are warranted. Recognition of an $IPAH_{mild\text{-}LD}$ phenotype also has implications for risk stratification, decisions regarding transplantation and PAH therapy clinical trial design.

IPAH with D_{LCO} <45%

Trip *et al* observed a bi-modal distribution of D_{LCO} %predicted in a cohort of 166 patients diagnosed with IPAH, and demonstrated that a D_{LCO} <45%predicted conferred worse survival (198). Whilst they included patients who had mild or moderate lung disease, we observed a similar distribution of D_{LCO} %predicted in patients without any lung disease ($IPAH_{no\text{-}LD}$, Figure 16). Olsson *et al* subsequently described a subgroup of patients with IPAH with no parenchymal lung disease but severely reduced gas transfer (199). In keeping with these two studies, our cohort of $IPAH_{no\text{-}LD}$ patients with D_{LCO} <45%predicted ($IPAH_{DLCO<45}$) was older, more likely to have a smoking history and had a lower exercise capacity. Although survival in patients with $IPAH_{DLCO<45}$ was significantly worse than those with $IPAH_{DLCO\geq45}$, significant improvements in ISWD were observed following PAH therapy, unlike in patients with $IPAH_{mild\text{-}LD}$. The cause of the reduced D_{LCO} in a proportion of IPAH patients is unclear. Pulmonary veno-occlusive disease is a rare cause of low D_{LCO} and is haemodynamically indistinguishable from PAH (195). However, we excluded patients (n=18) where there was a possibility of PVOD based on radiological assessment. Given the increased frequency of smoking in the $IPAH_{DLCO<45}$ group it is possible that the reduced D_{LCO} may represent emphysema not visible on cross-sectional imaging (200). Tobacco smoke has, however, also been shown to cause pulmonary vascular remodelling in animal models, and specifically to cause damage to the pulmonary capillaries (201). The data from the current study therefore provide further support for the existence of a *vanishing capillary syndrome* as proposed by Hoeper *et al* (21). Further histological data are required to fully explain this phenomenon.

Limitations

This is a retrospective study and hence there were some data availability issues including first follow-up ISWD data which was not available in 19% of patients. Patients who were unable to attempt the incremental shuttle walking test due to their pulmonary hypertension were ascribed a distance of 0m

which would minimise any potential bias resulting from missing data. Baseline scores for emPHasis-10 were only available for 34% of patients since it was only introduced in our centre in 2014. A small number of patients (3%) with $IPAH_{no\text{-}LD}$ and $IPAH_{mild\text{-}LD}$ did not have spirometry available and were categorised based on CT data alone. Parenchymal lung disease assessment was based on qualitative clinical reports provided by radiologists at the time of initial diagnosis in our unit, and not on fully quantitative assessments. Our data do, however, demonstrate that "real-world" clinical radiological assessments of the presence and extent of parenchymal lung disease can be used to identify patients groups with different outcomes. Whilst our patients now routinely undergo high resolution CT (HRCT) imaging and CT pulmonary angiography, some patients did not have specific HRCT imaging and so assessment of lung parenchyma in these patients may have been more limited. As there was no control group in this study, we cannot rule out a treatment effect of PAH therapies on patients with $IPAH_{mild\text{-}LD.}$

4.6 Conclusion

The presence of even mild parenchymal lung disease in patients who, based on current recommendations would be classified as having IPAH, has a significant adverse effect on survival and, in this patient cohort, was associated with a lack of significant improvement in exercise capacity following treatment. Patients with the phenotype of $IPAH_{mild\text{-}LD}$ can be identified using lung function testing and qualitative clinical description of the presence and extent of parenchymal lung disease on routine radiological reporting. In addition, a proportion of patients with IPAH and no evidence of lung disease or PVOD have a severely reduced diffusion capacity. Our data support the need for prospective RCTs in patients with these phenotypes to assess the effects of PAH therapies on short and long-term outcomes.

5. Identification of cardiac MRI thresholds for risk stratification in pulmonary arterial hypertension

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What this study adds to the literature

Improvement to, and maintenance of, a low-risk profile (<5% mortality/year) is the current goal of treatment strategies in patients with pulmonary arterial hypertension. We have identified and tested cardiac MRI thresholds to risk stratify patients at baseline and at follow-up. Cardiac MRI when used as a sole risk stratification tool can identify a high percentage of patients at low-risk of one-year mortality and when used in conjunction with current risk stratification approaches can improve risk stratification.

5.1 Abstract

Aims

Pulmonary arterial hypertension is a life-shortening condition. The European Cardiac and Respiratory Societies (ESC/ERS) and REVEAL 2.0 risk score calculator identify thresholds to predict 1-year mortality. This study evaluates whether cardiac-MRI thresholds can be identified and used to aid risk stratification and facilitate decision making.

Methods

Consecutive patients with pulmonary arterial hypertension (n=438) undergoing cardiac-MRI were identified from the ASPIRE-MRI database. Thresholds were identified from a discovery cohort and evaluated in a test cohort.

Results

A right ventricular-end-systolic-volume-index-%predicted threshold of 227% or a left ventricular-end-diastolic-volume-index of 58ml/m^2 identified patients at low (<5%) and high (>10%) risk of 1-year mortality. These metrics identified 63% and 34% of patients as low risk, respectively. A right ventricular ejection fraction >54%, 37-54% and <37% identified 21%, 43% and 36% of patients at low, intermediate and high-risk of 1-year mortality, respectively. At follow-up cardiac-MRI patients who improved to, or were maintained in a low risk group had a one-year mortality <5%. Right ventricular-end-systolic-volume-index-%predicted independently predicted outcome and when used in conjunction with the REVEAL 2.0 risk score calculator or a modified French Pulmonary Hypertension registry approach improved risk stratification for one-year mortality.

Conclusion

Cardiac-MRI can be used to risk stratify patients with pulmonary arterial hypertension using a threshold approach. Right ventricular-end-systolic-volume-index-%predicted can identify a high percentage of patients at low-risk of one-year mortality and when used in conjunction with current risk stratification approaches it can improve risk stratification. This study supports further evaluation of cardiac-MRI in risk stratification in PAH.

5.2 Introduction

Pulmonary arterial hypertension (PAH) is a rare and life-shortening condition (9). Without treatment, life-expectancy is less than 3 years (84), but with therapy, 5-year survival exceeds 60% in patients with idiopathic PAH (91, 193, 202). Current licensed therapies directed at the pulmonary vasculature target three pathways (203). There is evidence of superiority of upfront dual (83) or sequential oral combination therapy (204, 205) over oral monotherapy, but decisions regarding escalation to more intensive treatments, as well as transplantation, can be challenging.

The European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines proposed a "traffic light" risk stratification score to aid physicians in treatment decisions, dividing patients into low risk ("green", <5%), intermediate risk ("amber", 5-10%), and high risk ("red", >10%) of mortality at one-year based on a number of modifiable variables (43). These include an assessment of symptoms, exercise capacity and right ventricular function (43, 140). Whilst the thresholds used for these variables were largely based on expert opinion, they have since been validated for PAH in three European registries (140, 142, 206). These studies demonstrated that patients who improved to a low-risk profile at follow-up had better outcomes than those who did not. Outcomes for patients remaining in the intermediate risk group were significantly worse than low-risk patients and current approaches aim to improve and maintain patients in the low-risk group (43, 207). Similar results were observed in the North American Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk score (26). Risk stratification approaches typically include multiple variables (43, 140), however, right ventricular function is thought to be the primary determinant of morbidity and mortality in PAH (121, 151). Cardiac magnetic resonance imaging (MRI) is the recognised gold-standard for assessment of right ventricular function (147, 208, 209). Whilst echocardiography is more widely available, cheaper and the most commonly used imaging modality for right ventricular assessment, it is limited by lack of inter and intra-observer reproducibility (210) and acoustic windows (147, 211, 212).

Whilst studies have demonstrated the prognostic value of cardiac MRI in PAH (150-152, 160, 213), cardiac changes evaluated by current risk stratification tools are limited to atrial and pericardial assessment. Cardiac MRI metrics which are known to be prognostic in PAH are not included in either the REVEAL 2.0 or ESC/ERS risk score (43, 138). We sought to identify whether cardiac MRI metrics could accurately risk stratify patients using the ESC/ERS criteria of three levels of risk, and whether thresholds could be used to aid risk stratification. Some of the results of this study have been previously reported in the form of an abstract.

5.3 Methods

Patients with PAH were identified from the ASPIRE (Assessing-the-Spectrum-of-Pulmonary hypertension-Identified-at-a-Referral-centre) cardiac MRI database between April 2012 and March 2017. Patients underwent systematic evaluation (94, 214), including echocardiography, blood testing, exercise testing, lung function testing, multimodality imaging and right heart catheterisation. Patients were required to have a mean pulmonary artery pressure (mPAP) ≥25mmHg and to have had a pulmonary arterial wedge pressure (PAWP) recorded and were excluded if PAWP >15mmHg. Patients with co-existing lung or left-heart disease were excluded. Patients were listed in date order of cardiac MRI scan and assigned in alternate date order to discovery or test cohorts.

MRI image acquisition and analysis

Cardiac cine MRI was performed on a 1.5T GE HDx MRI scanner using an 8 channel receiver array and multi-slice balanced steady state imaging with retrospective gating (20 frames/cardiac cycle; slice thickness 8 mm; field of view 48; matrix 256 x 256; band width 125 kHz/pixel; repetition time/echo time TR/TE, 3.7/1.6 ms). A stack of images in the short-axis plane with slice thickness of 8 mm, 2mm inter-slice distance) were acquired covering both ventricles from base to apex. End-systole was considered to be the smallest cavity area. End-diastole was defined as the first cine phase of the R-wave triggered acquisition or largest volume.

Image analysis was performed by operators blinded to diagnosis and cardiac catheter result. Endocardial and epicardial surfaces were manually traced on short axis imaging to obtain end-systolic and end-diastolic volumes for the right ventricle (RVESV, RVEDV) and left ventricle (LVESV, LVEDV). Trabeculations for the chambers were not separately traced, and were included as part of the volume cavity measurement (171). Right ventricular ejection fraction (RVEF) was calculated from these volume measurements as previously described (157). Volumes were indexed for body surface area (RVESVi, RVEDVi, LVESVi, LVEDVi), and then corrected for age and sex and displayed as percent-predicted, as previously described (159). Ventricular mass index was calculated as RV mass divided by LV mass (172). Pulmonary artery relative area change was measured on the magnitude images of phase contrast images and calculated as (maximum pulmonary arterial area – minimal pulmonary arterial area)/minimal pulmonary arterial area. Phase contrast imaging parameters were as follows: repetition time TR/TE 5.6/2.7ms; slice thickness 10 mm; field of view 48 cm, bandwidth 62.5 kHz; matrix 256 3128; 40 reconstructed cardiac phases; and velocity encoding of flow 150 cm/s. Patients were in the supine position with a surface coil and with retrospective ECG gating.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 25 and R software. In this paper, a quintile refers to values which divide a ranked population into five equal groups. A quintile group refers to the population defined by the quintile. Data for continuous variables are presented as mean ±SD, and categorical data are presented as absolute values. Once thresholds were derived, volumes and values expressed as percentage-predicted were rounded to the nearest whole integer. Patients who had undergone lung transplantation were censored at the time of surgery; all other surviving patients were censored on 28th February 2019. Survival curves were assessed using the log-rank test.

Discovery cohort

In the discovery cohort, cardiac MRI parameters were assessed for significance for one-year mortality using univariate Cox regression analysis. A p value of <0.05 was considered statistically significant. Metrics significant at univariate analysis were utilised to identify thresholds. In order to identify thresholds, continuous variables were categorised into quintile groups for each metric. The quintiles were used as inclusive thresholds, and were taken to two decimal places, unless further precision was required. In each quintile group, one-year percentage mortality was calculated. Contiguous quintile groups sharing the same level of 1-year mortality (<5%, 5-10%, >10%) were combined.

Test cohort

The derived thresholds were applied to the test cohort. For each metric, if the corresponding group did not have the same level of risk, no further analysis was undertaken i.e. only those variables that showed consistency of risk were retained.

Whole cohort

Univariate and multivariate analysis of demographics, haemodynamics and MRI parameters was performed using Cox regression analysis. Locally estimated scatterplot smoothing (LOESS) regression analysis was performed on the whole cohort for percentage mortality at one year, for MRI metrics where consistency of risk was identified.

Follow-up data

Follow-up data were obtained for patients who had undergone a further cardiac MRI after a minimum of 3 months and before 31st March 2017.

Combination with other risk stratification tools

The REVEAL 2.0 Risk Score and number of low-risk criteria by the French Pulmonary Hypertension Registry (FPHR) approach were calculated in order to determine whether cardiac MRI could further stratify risk. This was performed in the incident population, maximising available data for each risk score. For the FPHR approach the 6-minute walking test distance threshold of 440 metres was substituted with a low-risk incremental shuttle walking test distance threshold of 330 metres (115, 215). Receiver operator characteristic (ROC) curve analysis was performed to compare approaches to risk stratification.

Mortality data

Mortality data were obtained from the NHS Personal Demographics Service, where electronic records are automatically updated when a death is registered in the UK. All patients on PAH therapies were followed up at our centre as part of the national service specification for patients with pulmonary hypertension. No patients were lost to follow-up.

Ethical approval was granted by the local ethics committee (STH14169; Assessing outcomes in patients with pulmonary arterial hypertension using cardiac MRI, ASPIRE Study 004).

5.4 Results

Between April 2012 and March 2017, 2008 patients were identified and 438 had PAH and met inclusion criteria (Figure 18). Demographic data are displayed in Table 11. At the time of cardiac MRI, 51% of patients were incident and treatment naïve and 49% prevalent. The mean age was 56.6 years and 75% were female. The majority (85%) had idiopathic PAH, heritable PAH or PAH in association with connective tissue disease. Portopulmonary hypertension and PAH in association with congenital heart disease comprised 14% of patients. The remainder had PAH related to HIV infection or induced by drugs and toxins.

During the course of the study 72% of patients received combination therapy (Table 11). A small number of patients, including nitric oxide vaso-responders maintained on calcium channel blockers, did not receive targeted treatment. Discovery and test-cohorts were well-matched and confidence intervals included the value zero for all continuous variables including cardiac MRI metrics (Table 11, Table 12).

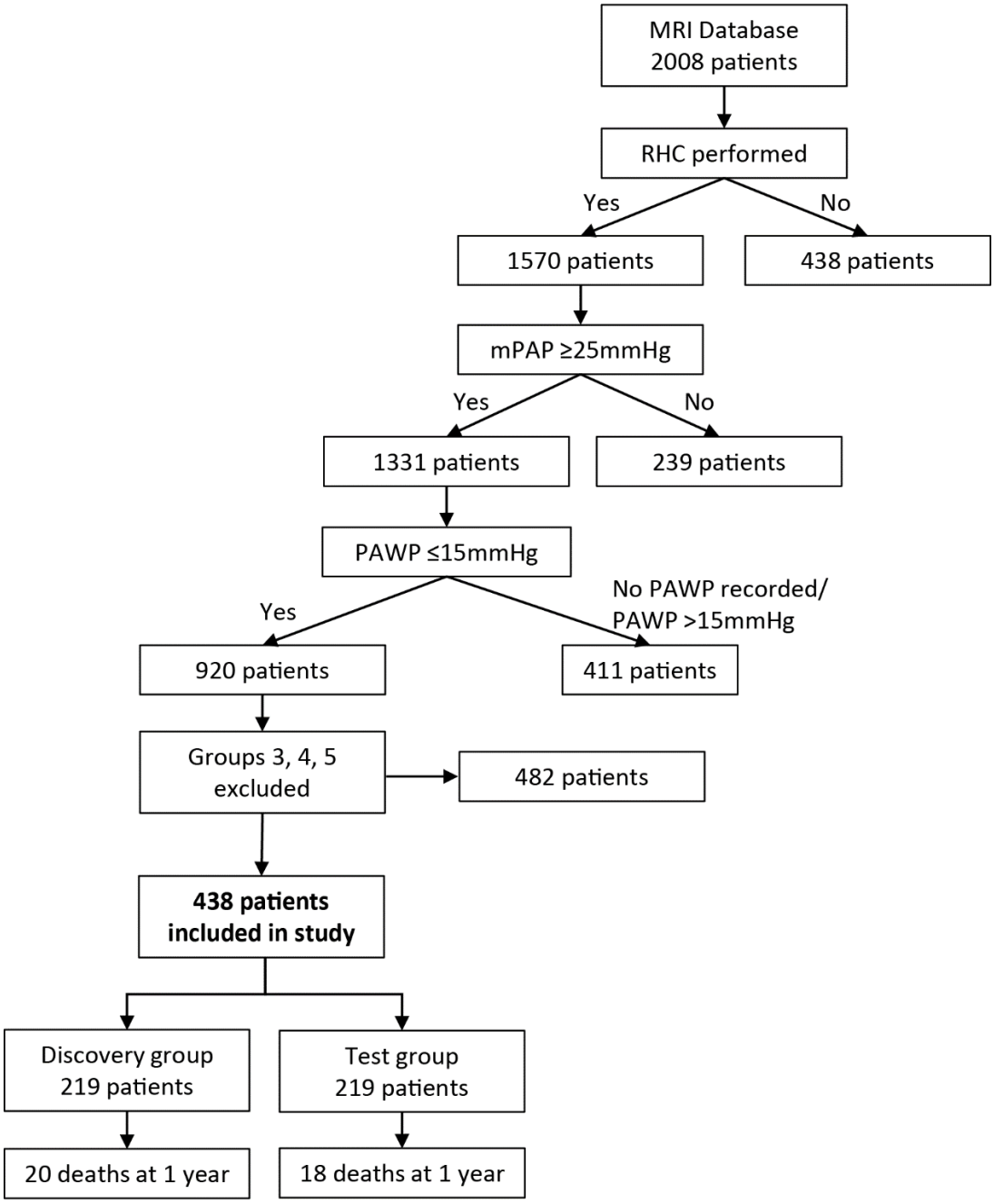

Figure 18: Flow chart demonstrating patients included and reasons for exclusion.

Abbreviations: RHC = right heart catheterisation, PAH = pulmonary arterial hypertension, LHD = left heart disease, PH = pulmonary hypertension, mPAP = mean pulmonary artery pressure, PAWP = pulmonary arterial wedge pressure.

Table 11: Baseline demographics in patients undergoing cardiac MRI

	All patients (438)	Discovery (219)	Test (219)
Demographics			
Age (years)	56.6 ±15.9	56.0 ±15.7	57.2 ±16.1
Gender F/M, (F %)	327/111 (75)	161/58 (74)	166/53 (76)
WHO FC I n (%)	7 (2)	4 (2)	3 (1)
WHO FC II n (%)	118 (27)	59 (27)	59 (27)
WHO FC III n (%)	261 (60)	128 (58)	133 (61)
WHO FC IV n (%)	52 (12)	28 (13)	24 (11)
Incident/Prevalent (I%)	225/213 (51)	109/110 (50)	116/103 (53)
ISWD (m)	231 ±194	237 ±196	223±193
PAH Subtype			
IPAH/HPAH n (%)	197 (45)	101 (46)	96 (44)
PAH-CTD n (%)	163 (37)	78 (36)	85 (39)
PAH-CHD n (%)	38 (9)	18 (8)	20 (9)
PoPH n (%)	25 (6)	16 (7)	9 (4)
Other n (%)	15 (3)	6 (3)	9 (4)
Maximal Treatment			
Nil-targeted n (%)	23 (5)	12 (6)	11 (5)
Oral monotherapy n (%)	100 (23)	46 (21)	54 (25)
Oral combination n (%)	205 (47)	101 (46)	104 (47)
Prostanoid +/- oral n (%)	110 (25)	60 (27)	50 (23)
Haemodynamics			
mRAP (mmHg)	10 ±5	10 ±5	10 ±5
mPAP (mmHg)	48 ±14	47 ±14	48 ±15
PAWP (mmHg)	11 ±3	11 ±3	11 ±3
CO (l/min)	5.0 ±1.8	5.1 ±1.8	4.9 ±1.8
CI (l/min/m^2)	2.8 ± 1.0	2.8 ±1.0	2.7 ±1.0
PVR (dynes/sec/cm^{-5})	711 ±447	688 ±432	735 ±462
SvO_2 (%)	65.4 ±10.1	66.3 ±9.9	64.5 ±10.3
Survival Analysis			
Dead at 1-year post CMRI n (%)	38 (8)	20 (9)	18 (8)

For all variables, the difference between 95% confidence intervals for the groups included the value zero.

RVESVi = right ventricular end-systolic volume, indexed for body surface are; RVEDVi = right ventricular end-diastolic volume, indexed for body surface area; RVEF = right ventricular ejection fraction; LVESVi = left ventricular end-systolic volume, indexed for body surface area; LVEDVi = left ventricular end-diastolic volume, indexed for body surface area; LVEF = left ventricular ejection fraction; VMI = ventricular mass index; PA = pulmonary artery; %pred = displayed as percent predicted for age and sex.

Table 12: Cardiac MRI metrics

Metric	All patients (438)	Discovery (219)	Test (219)
Right sided measurements			
RVESVi (ml/m^2)	53.0 ±27.0	54.5 ±26.9	51.5 ±27.1
RVEDVi (ml/m^2)	88.6 ±33.5	89.9 ±33.7	87.3 ±33.7
RVESVi %pred	220.0 ±117.7	225.6 ±122.7	214.4 ±112.5
RVEDVi %pred	120.4 ±45.3	121.9 ±46.7	118.9 ±44.0
RVEF	42.0 ±13.3	41.0 ±13.6	43.0 ±13.0
RVEF %pred	62.7 ±20.1	61.4 ±20.7	64.0 ±19.4
Left sided measurements			
LVESVi (ml/m^2)	17.3 ±8.2	17.9 ±9.1	16.7 ±7.1
LVEDVi (ml/m^2)	54.0 ±16.1	54.6 ±17.0	53.4 ±15.1
LVESVi %pred	71.8 ±33.8	74.1 ±38.3	69.6 ±28.4
LVEDVi %pred	73.0 ±21.5	73.5 ±22.8	72.5 ±20.2
LVEF	68.3 ±10.0	67.7 ±10.6	68.9 ±9.4
LVEF %pred	100.9 ±14.7	100.2 ±15.7	101.7 ±13.7
Miscellaneous			
VMI	0.529 ± 0.297	0.528 ±0.296	0.531 ±0.299
PA relative area change (%)	11.99 ±8.70	12.39 ±9.20	11.57 ±8.15

For all continuous variables, the difference between 95% confidence intervals for the groups included the value zero.

WHO FC = World Health Organisation functional class; ISWD = incremental shuttle walking test distance; PAH = pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; HPAH = heritable pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PoPH = portopulmonary hypertension. Haemodynamics measure at right heart catheterisation: mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; CO = cardiac output; CI = cardiac index; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; CMRI = cardiac magnetic resonance imaging.

Table 13: Univariate and multivariate analysis on whole cohort (scaled)

	n	Univariate Hazard Ratio	*P* value	Multivariate Hazard Ratio	*P* value
Demographics					
Age >50	438	3.576	0.008		
Sex (F)	438	0.562	0.086		
WHO FC I and II vs III and IV	430	2.724	0.037		
IPAH		0.534	0.079		
PAH-CTD		3.017	0.001		
PAH-CHD		0.195	0.269		
ISWD (m)	398	0.174	<0.001	0.162	<0.001
Haemodynamics					
mRAP (mmHg)	224	1.55	0.006		
mPAP (mmHg)	224	1.254	0.263		
MvO2 (%)	224	0.458	<0.001		
Cardiac Index (l/min/m^2)	224	0.506	0.016		
PVR (dynes/sec/cm^{-5})	224	1.5	0.06		
Other parameters					
eGFR <60 (ml/min/1.73m^2)	436	3.104	<0.001		
SBP <110 (mmHg)	217	1.025	0.968		
Heart Rate >96	417	4.123	0.001		
Pericardial effusion present	438	3.323	0.001		
Recent hospitalisation (6m)	438	1.822	0.071		
MRI metrics					
RVEDVi	438	1.285	0.07		
RVEDVI %pred	438	1.426	0.011		
RVESVi	438	1.392	0.011		
RVESVI %pred	438	1.616	<0.001	1.571	0.025
LVEDVi	438	0.451	<0.001		
LVEDVI %pred	438	0.435	<0.001		
LVESVi	438	0.601	0.016		
LVESVI %pred	438	0.598	0.066		
RVEF	438	0.634	0.005		
LVEF	438	0.847	0.275		
RVEF %pred	438	0.586	0.001		
LVEF %pred	438	0.795	0.16		
PA relative area change (%)	438	0.642	0.029		
VMI	438	1.125	0.446		

Hazard ratios for continuous variables are scaled by dividing individual values by the standard deviation (z-score). Due to the limited number of events, only 6 variables were entered into the multivariate analysis reflecting measures of symptoms, exercise capacity, markers of haemodynamic

severity and right ventricular function. WHO FC, ISWD, mRAP, Cardiac Index, RVESVi %pred and RVEF were significant at univariate analysis and were entered into the multivariate model.

WHO FC = World Health Organisation functional class; IPAH = idiopathic pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; ISWD = incremental shuttle walking test distance; mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; MvO2 = mixed venous oxygen saturation; PVR = pulmonary vascular resistance; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; RVEDVi = right ventricular end-diastolic volume, indexed for body surface area; RVESVi = right ventricular end-systolic volume, indexed for body surface area; LVEDVi = left ventricular end-diastolic volume, indexed for body surface area; LVESVi = left ventricular end-systolic volume, indexed for body surface area; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; PA = pulmonary artery; VMI = ventricular mass index; %pred = displayed as percent predicted for age and sex.

Table 14: Univariate analysis in Discovery Cohort

Metric	Univariate Hazard Ratio	*p* value	n
RVESVi (ml/m^2)	1.016	0.022	219
RVEDVi (ml/m^2)	1.009	0.150	219
RVESVi %pred	1.004	0.002	219
RVEDVi %pred	1.008	0.045	219
RVEF %	0.955	0.008	219
RVEF %pred	0.966	0.003	219
LVESVi (ml/m^2)	0.935	0.055	219
LVEDVi (ml/m^2)	0.936	0.000	219
LVESVi %pred	0.987	0.113	219
LVEDVi %pred	0.957	0.000	219
LVEF %	0.974	0.142	219
LVEF %pred	0.980	0.085	219
VMI	2.728	0.140	210
PA Relative Area Change (%)	0.956	0.121	219

Abbreviations: RVESVi = right ventricular end-systolic volume, indexed for body surface area; RVEDVi = right ventricular end-diastolic volume, indexed for body surface area; RVEF = right ventricular ejection fraction; LVESVi = left ventricular end-systolic volume, indexed for body surface area; LVEDVi = left ventricular end-diastolic volume, indexed for body surface area; LVEF = left ventricular ejection fraction; VMI = ventricular mass index; PA = pulmonary artery; %pred = displayed as percent predicted for age and sex.

Table 15: Percentage mortality at 4, 6 and 12 months by quintile group

	Discovery Cohort			
	n =	% mortality		
		4 months	**6 months**	**12 months**
RVESVi (ml/m²)				
<30.48	43	0	2.3	2.3
30.48-41.75	44	2.3	2.3	4.5
41.76-54.28	44	4.5	9.1	9.1
54.29-76.12	45	2.2	4.4	13.3
>76.12	43	7	14	16.3
RVESVi %pred				
<124.09	43	2.3	2.3	2.3
124.09-166.11	44	2.3	4.5	6.8
166.12-226.71	44	0	2.3	2.3
226.72-318.53	44	2.3	6.8	11.4
>318.53	44	9.1	15.9	22.7
RVEDVi %pred				
<83.15	43	4.7	9.3	9.3
83.15-98.75	44	0	0	2.3
98.76-120.07	44	0	2.3	2.3
120.08-158.67	44	9.1	13.6	20.5
>158.67	44	2.3	6.8	11.4
RVEF %				
<27.01	43	4.7	11.6	14
27.01-37.35	44	6.8	11.4	15.9
37.36-44.20	44	2.3	6.8	9.1
44.21-54.00	45	2.2	2.2	6.7
>54.00	43	0	0	0
RVEF %pred				
<40.869	43	4.7	11.6	14
40.869-54.974	42	4.5	11.4	15.9
54.975-67.366	44	4.5	6	9.1
67.367-81.872	43	2.3	2.3	6.8
>81.872	44	0	0	0
LVEDVi (ml/m²)				
<39.24	43	4.7	14	23.3
39.24-48.71	44	6.6	11.4	11.4
48.72-57.68	44	4.5	6.8	11.4
57.69-69.27	44	0	0	0
>69.27	44	0	0	0
LVEDVi %pred				
<51.66	43	7	16.3	25.6
51.66-66.05	44	6.8	9.1	9.1
66.06-77.33	44	2.3	4.5	6.8
77.34-93.64	44	0	2.3	4.5
>96.64	44	0	0	0

Abbreviations: RVESVi = right ventricular end-systolic volume, indexed for body surface area; RVEDVi = right ventricular end-diastolic volume, indexed for body surface area; RVEF = right ventricular ejection fraction; LVEDVi = left ventricular end-diastolic volume, indexed for body surface area; %pred = displayed as percent predicted for age and sex.

Survival Analysis

At one year post cardiac MRI 38 patients (8.7%) had died; 20 patients (9.1%) in the discovery-cohort and 18 patients (8.2%) in the test-cohort. Patients aged >50 years were more likely to die at one year (p=0.008), as were those with PAH-CTD (p=0.001); univariate and multivariate analysis for the whole cohort is shown in Table 13. Results of Cox-regression analysis for cardiac MRI variables in the discovery cohort, based on survival at one year, are shown in Table 14.

Discovery and Test Cohort

Quintile groups for each cardiac metric in the discovery group are displayed in Table 15. Calculated one-year mortality per quintile group is presented in graphical form (Figure 19).

Derived thresholds were applied to the test cohort Table 16. Levels of risk were non-concordant between the discovery and test cohorts for RVESVi, RVEDVi %predicted, RVEF %predicted and LVEDVi %predicted (highlighted in blue) and excluded from further analysis.

Three variables were concordant for levels of risk. Using a threshold of RVESVi %predicted of 227%, patients could be stratified into a low-risk group (one-year mortality 4.3%), and high-risk group (one-year mortality 15%). The low-risk group (those with an RVESVi %predicted below this threshold) represented 63% of the test cohort (56% of incident patients and 72% of prevalent patients; Figure 20). Left ventricular end-diastolic volume index stratified patients into a low-risk group (one-year mortality 2.7%), and high-risk group (one-year mortality 11%) using a threshold of 58ml/m^2. The low-risk group (those with an LVEDVi above this threshold) represented 34% of the test cohort (26% of incident patients and 43% of prevalent patients). Right ventricular ejection fraction stratified patients into low (one-year mortality 4.4%), intermediate (7.4%) and high (11.4%) risk groups using thresholds of >54%, 37-54% and <37%, respectively. Using RVEF, 21% of the test cohort were identified as low risk, 43% intermediate risk and 36% high risk.

When the analysis was repeated and patients with congenital heart disease excluded, thresholds for RVEF and LVEDVi were unchanged. The threshold for RVESVi %predicted changed from 227% to 225%.

There was no evidence of significant collinearity between LVEDVi, RVESVi %predicted and RVEF.

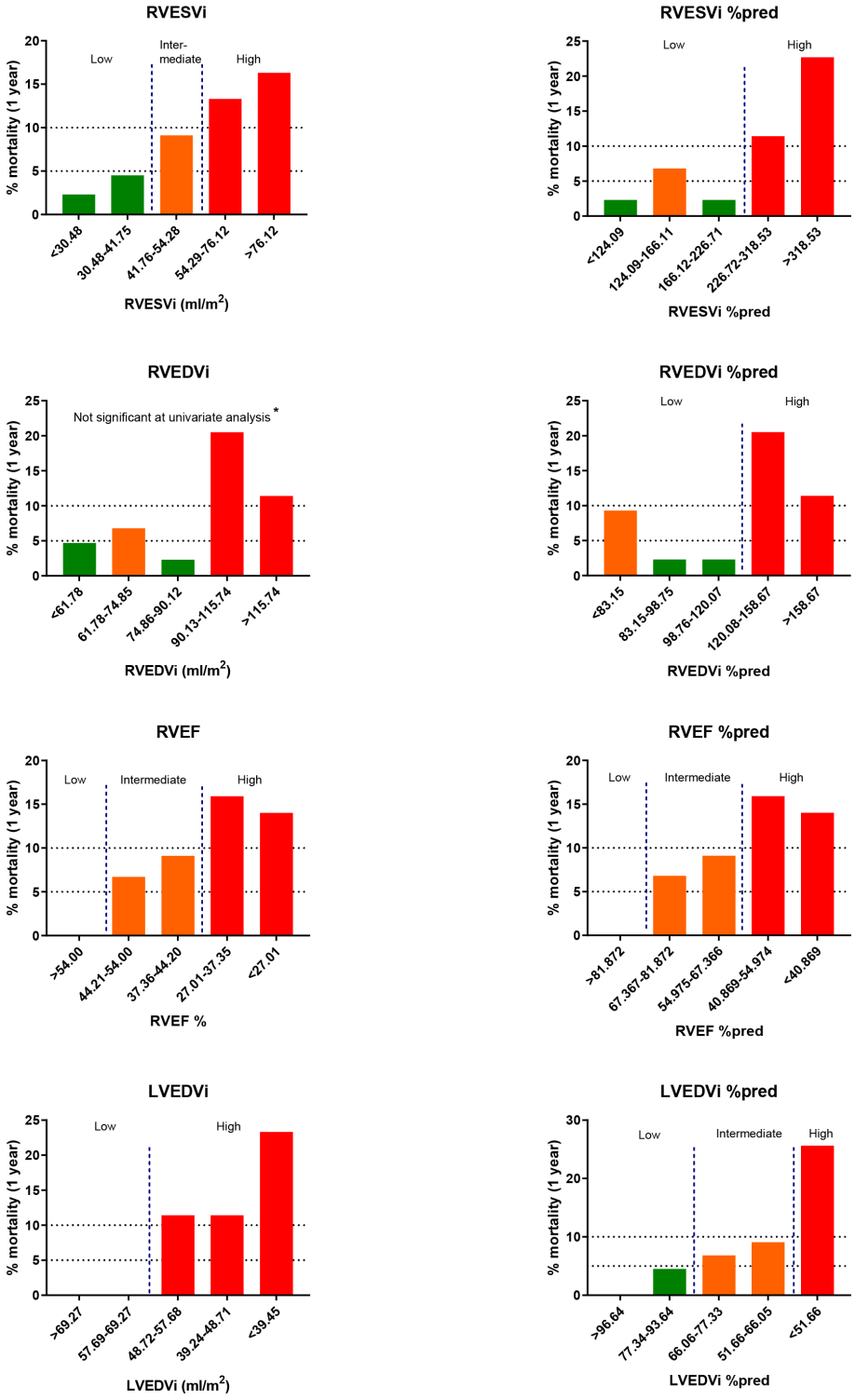

*Figure 19: Histograms displaying quintile groups and percentage mortality at one year for cardiac MRI variables (discovery). Blue dashed line represents division into categories of risk. *RVEDVi was not significant at univariate analysis and division into risk categories was not performed.*

Abbreviations: RVESVi = right ventricular end-systolic volume, indexed for body surface area; RVEF = right ventricular ejection fraction; LVEDVi = left ventricular end-diastolic volume, indexed for body surface area; %pred = displayed as %predicted for age and sex.

Table 16: Percentage mortality at 4, 6 and 12 months

	Test Cohort				Corresponding risk category in Discovery cohort
	n =	% mortality			
		4 months	6 months	12 months	
RVESVi (ml/m²)					
<41.76	100	2	4	6	Low (<5%)
41.76-54.28	35	0	0	0	Intermediate (5-
>54.29	84	8.3	8.3	14.3	High
RVESVi %pred					
<226.72	139	1.4	2.9	4.3	Low
>226.72	80	8.8	8.8	15	High
RVEDVi %pred					
<120.08	134	3	4.5	6	Low (<5%)
>120.08	85	5.9	5.9	11.8	High
RVEF %					
<37.36	79	6.3	6.3	11.4	High
37.36-54.00	95	3.2	5.3	7.4	Intermediate
>54.00	45	2.2	2.2	4.4	Low
RVEF %pred					
<54.975	76	7.9	7.9	13.2	High
54.975-81.872	101	1	3	5	Intermediate
>81.872	42	4.8	4.8	7.1	Low (<5%)
LVEDVi (ml/m²)					
<57.69	145	5.5	6.9	11	High
>57.69	74	1.4	1.4	2.7	Low
LVEDVi %pred					
<51.66	28	7.1	7.1	17.9	High
51.66-77.33	105	3.8	4.8	6.7	Intermediate
>77.33	86	3.5	4.7	7	Low (<5%)

Abbreviations: RVESVi = right ventricular end-systolic volume, indexed for body surface area; RVEDVi = right ventricular end-diastolic volume, indexed for body surface area; RVEF = right ventricular ejection fraction; LVEDVi = left ventricular end-diastolic volume, indexed for body surface area; %pred = displayed as percent predicted for age and sex. Blue highlighting indicates non-concordance for levels of risk between discovery and test cohorts.

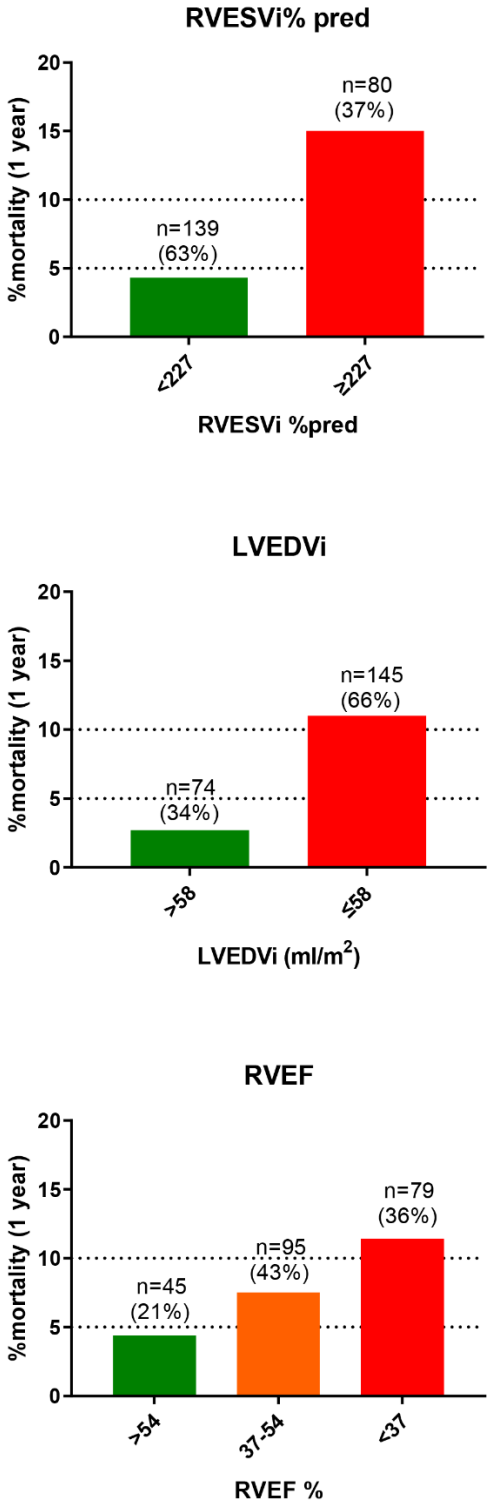

Figure 20: Histograms displaying percentage mortality at one year for derived thresholds for cardiac MRI variables (test cohort).

Abbreviations: RVESVi = right ventricular end-systolic volume indexed for body surface area; RVEF = right ventricular ejection fraction; LVEDVi = left ventricular end-diastolic volume, indexed for body surface area; %pred = displayed as percent predicted corrected for age and sex.

Follow up data

Follow-up cardiac MRI was performed in 165 patients. At follow-up, RVESVi %predicted and RVEF were able to risk stratify patients based on thresholds identified in the discovery cohort. Using RVESVi %predicted for those who remained in low risk (RVESVi %predicted <227%) or improved to low risk (67% of patients in total), the one-year survival was 96.3%, and for those who remained high risk or deteriorated to high risk (33% of patients in total) the one-year survival was 87.3% (Figure 21). Right ventricular ejection fraction was able to stratify patients into high and low-risk of one-year mortality at follow-up. Patients with an RVEF of <37% (25% of patients) had a one-year survival of 83.3% whereas patients with an RVEF of 37-54% (45% of patients) and >54% (29% patients) had one-year survival of 97.3% and 95.8% respectively.

Combining cardiac MRI with REVEAL and FPHR scores

The REVEAL 2.0 and modified FPHR scores, in isolation and in combination with RVESVi %predicted, are displayed for the incident population (n=224) in Figure 22. For REVEAL 2.0 all patients had at least 11 of the 13 parameters available, and for modified FPHR there were no missing data. In those with a REVEAL 2.0 score ≥8, and in those determined to be either intermediate or high-risk by the modified FPHR approach, RVESVi %predicted reclassified patients into higher or lower risk categories (Figure 22).

Based on REVEAL 2.0 ≤6 for low, 7-8 for intermediate, and ≥9 for high-risk categories (138), and using a dichotomised score of +2 or -2 for RVESVi %predicted threshold of 227%, MRI reclassified 47% of patients, 36% (n=82) of patients into a lower risk group and 11% (n=25) into a higher risk group.

Receiver operating characteristic (ROC) curves are displayed in Figure 23. For the REVEAL 2.0 score, addition and subtraction of 2 points for RVESVi %predicted ≥227% and <227%, respectively, increased the c-statistic from 0.74 (95% CI, 0.65-0.83) to 0.78 (95% CI 0.70-0.87). Using the modified FPHR approach the c-statistic increased from 0.70 (95% CI 0.59-0.80) to 0.74 (0.63-0.84) by adding an additional point for patients with a RVESVi %predicted <227%.

Verification of thresholds

For LVEDVi, RVESVi %pred and RVEF, LOESS regression analysis confirmed that identified thresholds were within the confidence intervals for the associated risk of 1-year mortality (Figure 24).

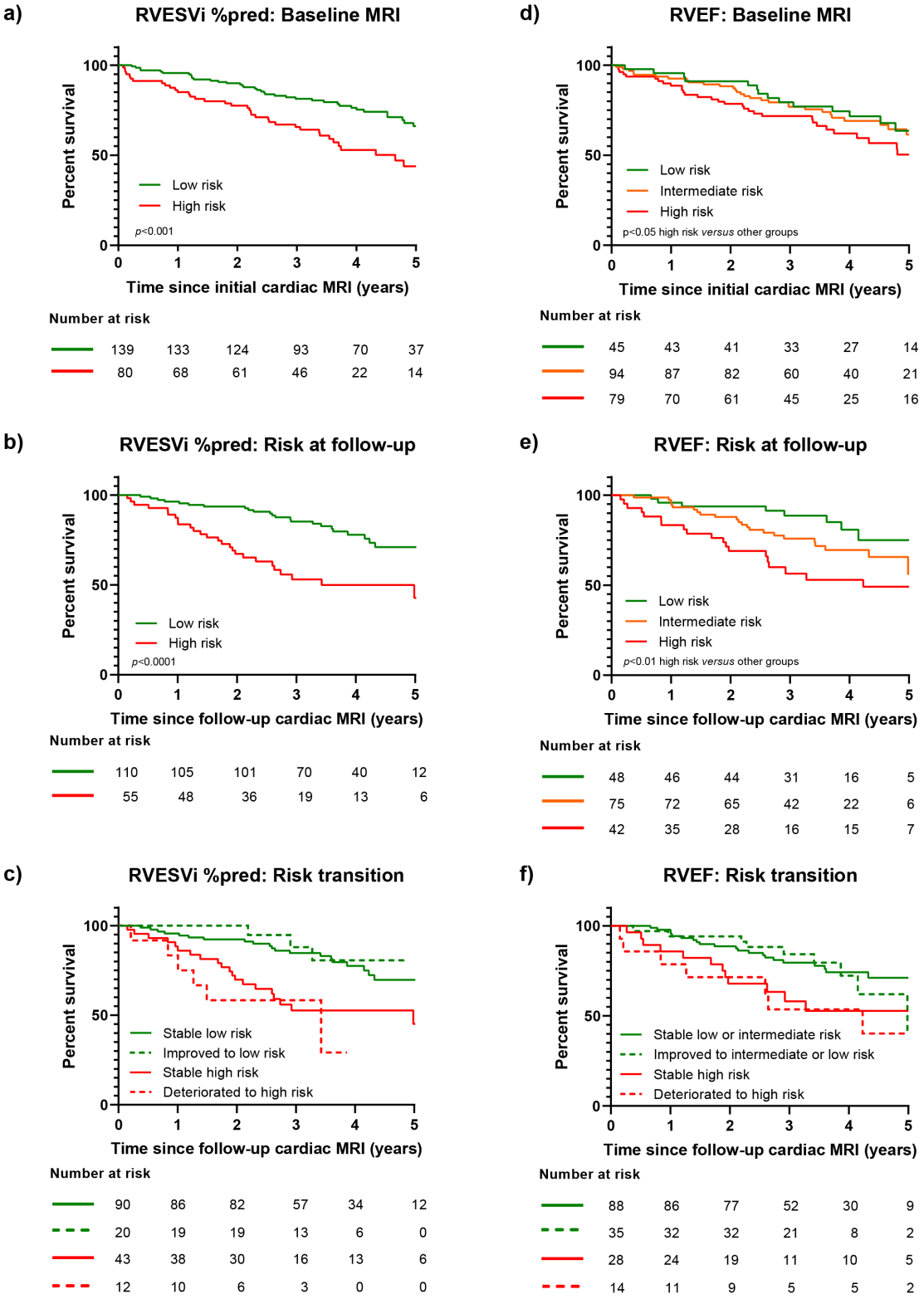

Figure 21: Kaplan Meier survival curves based on cardiac MRI thresholds for a) RVESVi %pred at baseline (test cohort); b) RVESVi %pred at follow-up cardiac MRI; c) transition of risk between baseline and follow-up cardiac MRI for RVESVi %pred; d) RVEF at baseline (test cohort); e) RVEF at follow-up cardiac MRI; f) transition of risk between baseline and follow-up cardiac MRI for RVEF.

Abbreviations: RVESVi = right ventricular end-systolic volume, indexed for body surface area; %pred = displayed as %predicted corrected for age and sex. RVEF = right ventricular ejection fraction.

			Reclassification following addition of MRI			
Reveal Risk Calculator 2.0			REVEAL with low-risk RVESVi%		REVEAL with high-risk RVESVi%	
	n (%)	1y mortality %	n (%)	1y mortality %	n (%)	1y mortality %
Reveal ≤ 6	25 (11)	0	16 (7)	0	9 (4)	0
Reveal 7	25 (11)	0	19 (8)	0	6 (3)	0
Reveal 8	36 (16)	6	26 (12)	0	10 (4)	20
Reveal 9	44 (20)	9	24 (11)	8	20 (9)	10
Reveal 10	33 (15)	15	12 (5)	8	21 (9)	19
Reveal 11	27 (12)	19	10 (4)	10	17 (8)	24
Reveal ≥12	34 (15)	24	14 (6)	7	20 (9)	35
Modified FPHR Low Risk Score			Mod. FPHR with low-risk RVESVi%		Mod. FPHR with high-risk RVESVi%	
3-4 criteria	74 (33)	4	56 (25)	4	18 (8)	6
1-2 criteria	132 (59)	12	60 (27)	3	72 (32)	19
0 criteria	18 (8)	27	5 (2)	20	13 (6)	31

Figure 22: Impact of adding cardiac MRI to widely used risk stratification approaches: REVEAL 2.0 and Modified French Pulmonary Hypertension Registry approach to ESC/ERS guidelines. Green = low risk of one-year mortality (<5%), amber = intermediate risk (5-10%) and red = high risk (>10%).Abbreviations: REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL); RVESVi = right ventricular end-systolic volume, indexed for body surface area; %pred = displayed as percent predicted for age and sex; FPHR = French Pulmonary Hypertension Registry

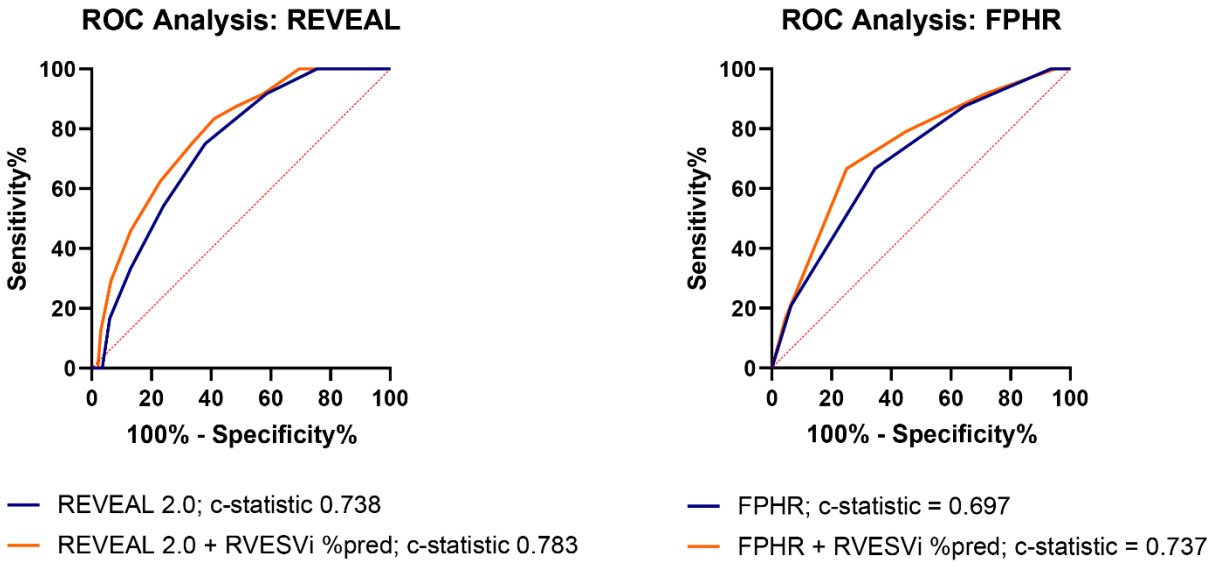

Figure 23: ROC curves showing potential added value of cardiac MRI in conjunction with risk stratification approaches: The REVEAL risk score calculator 2.0 (left) and modified French Pulmonary Hypertension Registry approach to risk stratification (right), using an RVESVi %predicted threshold of 227%

Abbreviations: ROC = receiver operating characteristic; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; RVESVi = right ventricular end-systolic volume, indexed for body surface area.

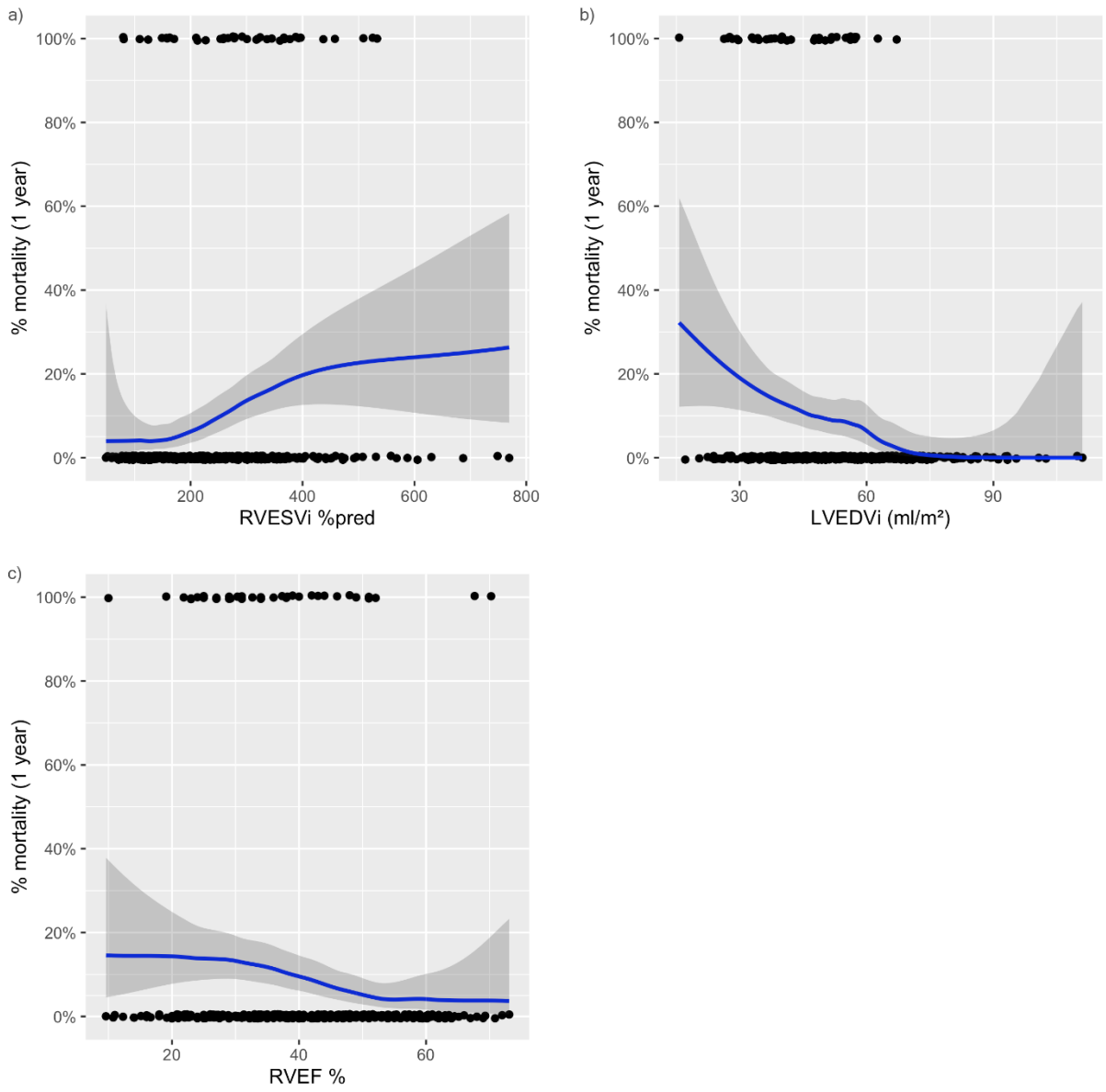

Figure 24: LOESS regression curve demonstrating predicted mortality at one-year for cardiac MRI parameters: a) RVESVi %predicted, b) LVEDVi, c) RVEF

Abbreviations: LOESS = locally weighted scatterplot smoothing; LVEDVi = left ventricular end-diastolic volume, indexed for body surface area; RVESVi = right ventricular end-systolic volume indexed for body surface area; RVEF = right ventricular ejection fraction; %pred = displayed as percent predicted corrected for age and sex; MRI= magnetic resonance imaging

5.5 Discussion

To our knowledge, this is the first study to identify cardiac MRI thresholds that can be used to risk stratify patients with PAH according to the ESC/ERS traffic light approach, at baseline and follow-up. Furthermore, the addition of right ventricular end systolic volume index % predicted independently predicted outcome and when used in conjunction with current approaches improved risk stratification.

A number of studies have demonstrated the prognostic value of cardiac MRI in PAH at baseline and follow-up (150-152, 160, 169, 213). In addition to volumetric measurements, right ventricular ejection fraction (RVEF), right ventricular to pulmonary artery (PA) coupling metrics and PA relative area change (151, 156, 216, 217) have also been shown to be prognostic. In this study we have confirmed the prognostic value of cardiac MRI but specifically we have identified and tested thresholds that may improve its clinical utility by allowing incorporation into risk stratification scores, which are increasingly used to inform treatment decisions (192).

Right ventricular ejection fraction is the most commonly reported cardiac MRI metric and this study confirms its prognostic value but also identifies thresholds that can be used to identify patients at low (RVEF >54%), intermediate (RVEF 37-54%) and high risk (RVEF<37%) of one-year mortality. The threshold of RVEF <35% in a previous study of 76 incident patients with PAH, identified as conferring a higher risk of mortality over a median follow-up period of 59 months (151), is similar to that identified in our study of <37% for high-risk patients. Using the ESC/ERS approach to risk stratification 21%, 43% and 36% of patients were identified at low, intermediate and high risk of one-year mortality in the test cohort, similar to the results of approaches using multiple non-invasive and invasive parameters to assess risk (142, 206). Thresholds identified from this study for RVEF could therefore be incorporated into the ESC/ERS risk stratification table to aid decision making.

In the present study, baseline volumetric measurements RVESVi %predicted and LVEDVi were both prognostic. We have previously demonstrated in a large study of 576 patients with PAH that RVESVi %predicted was the cardiac MRI measurement with the strongest prognostic value (157) and in this study also independently predicted outcome. However, it is important to recognise that right ventricular volumes decrease with advancing age, are larger in men and increase with body surface area (218). Our group and others have previously identified the need to adjust cardiac MRI variables for age, sex and body surface area (157, 159, 219) and this study demonstrates for right ventricular volumes that correction for these variables is important when risk stratifying patients. In this study pulmonary artery relative area change did not predict short term mortality (one year), whereas it did

predict mortality during the duration of this study ($p<0.005$). This highlights that MRI metrics that measure right ventricular function may be more helpful in defining short term mortality.

Whereas for RVEF we were able to identify low, intermediate and high risk of one-year mortality, using volumetric measurements RVESVi %predicted and LVEDVi we were only able to identify patients at low and high-risk of one-year mortality. Thresholds for RVESVi %predicted <227% and LVEDVi >58ml/m^2 identified low-risk patients. An LVEDVi threshold of <40ml/m^2 has previously been used to identify patients at increased risk of mortality (152), but our study suggests that a LV volume of ≤58ml/m^2 confers a high risk of mortality at one year. Using a threshold for RVESVi %predicted of <227% and for LV volume of >58ml/m^2, 63% and 34% of patients could be identified at low risk of one-year mortality, respectively. Right ventricular ejection fraction identified 21% and 43% of patients as low risk and intermediate risk, respectively.

Treatment strategies are currently based on maintaining or improving patients to a low-risk group and a dichotomised score identifying a low and high-risk group may be a preferable approach to informing and simplifying treatment decisions. In particular, data from a number of studies has demonstrated that patients identified as intermediate risk using current risk stratification scores have a significantly worse survival than low-risk patients. Identification and maintenance of a low-risk status remains the goal of current treatment strategies. A number of registry studies have shown that in patients whose risk profile can be modified to low risk, outcomes are significantly improved (26, 206). However, registry analysis using current approaches to risk stratification has only identified small numbers of patients in this low-risk category at presentation (12% of patients in the COMPERA and 23% in the Swedish Registry). At follow-up more patients achieved low-risk status (24% in COMPERA, 39% in the Swedish and 42% in the French Registry). In contrast, in this study using RVESVi %predicted, 63% of patients overall could be identified as low risk in the test cohort with 56% of incident (newly diagnosed patients) and 72% of prevalent patients (following initiation of treatment). The one-year mortality of all incident patients in this registry was 10.7% compared to 11.0% in COMPERA and 14% in the Swedish Registry, whilst for prevalent patients the one-year mortality was 6.6% in our cohort, 10.3% in COMPERA and 9% in the Swedish Registry. Whereas the French registry included idiopathic, heritable and drug-induced PAH, the COMPERA, Swedish and our own registry also included patients with other forms of PAH, predominantly related to connective tissue diseases. The haemodynamic parameters of our patients were similar to those in COMPERA and French registries although COMPERA includes a smaller proportion of patients in WHO Functional Class II. The enrolment period in our study is more recent and over 70% of patients received combination therapy. Nonetheless at diagnosis cardiac MRI was able to identify a high percentage of patients at low risk (56%). Our findings suggest that assessing right ventricular function using gold standard techniques may be preferable to other investigative

approaches, if identification of patients at low risk of one-year mortality is the goal. Further study is required to test this hypothesis. Using thresholds identified in the discovery cohort we have also demonstrated that cardiac MRI measurements can be used at follow-up to risk stratify patients and that improvement to low risk or maintenance of patients in a low-risk group is strongly prognostic.

Finally, we have assessed how cardiac MRI could be used in conjunction with current risk stratification approaches; RVESVi %predicted, when used in conjunction with REVEAL 2.0 and modified FPHR, was able to further risk stratify patients. For patients classified as low risk by the modified FPHR or with a REVEAL 2.0 ≤6, MRI did not impact on risk stratification. However, when used in conjunction with the REVEAL 2.0 risk calculator and using a dichotomised score of +2 or -2 points for a RVESVi %predicted threshold of 227%, for patients with a REVEAL 2.0 score >6, MRI was able to reclassify 36% of patients into a lower risk group, and 11% of patients into a higher risk group.

Limitations

Our approach to identify thresholds for risk stratification using quintile groups in the discovery cohort is a valid but empiric approach. If the sample size was larger, other cardiac MRI parameters may have been identified. Like the COMPERA and Swedish registries we included patients with congenital heart disease. Although, repeat analysis with these patients excluded identified unchanged or similar thresholds, we would recommend further study in congenital heart disease and thresholds in this study should be used with caution in this population. The aim of this study was to assess whether a threshold approach can be used to risk stratify patients using MRI and the methodology used may not have identified “optimal” thresholds. Our findings would benefit from external validation.

5.6 Conclusion

Thresholds derived from cardiac MRI metrics may be used to risk stratify patients with PAH. This registry has identified that cardiac MRI, when used as a sole risk stratification tool, identifies a high percentage of patients at low-risk of one-year mortality and when used in conjunction with current risk stratification approaches can improve risk stratification.

6. Maximal exercise testing and risk stratification in pulmonary arterial hypertension

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Subject: Pulmonary Hypertension: Risk-stratification; incremental exercise testing; outcome

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What is already known

The incremental shuttle walking test is a maximal exercise test, correlates with pulmonary haemodynamics and in pulmonary arterial hypertension does not demonstrate a ceiling effect.

What this study adds

Thresholds from the incremental shuttle walking test can be used to risk-stratify patients with pulmonary arterial hypertension and, unlike sub-maximal walking tests, an improvement in maximal exercise capacity independently predicts survival.

6.1 Abstract

Exercise capacity predicts mortality in pulmonary arterial hypertension but limited data exist on the routine use of maximal exercise testing. This study evaluates a maximal test, the incremental shuttle walking test, and assesses its utility in risk stratification in pulmonary arterial hypertension.

Consecutive patients with pulmonary hypertension were identified from the ASPIRE registry from 2001 to 2018. Thresholds for levels of risk were identified at baseline, tested at follow-up and their incorporation into current risk stratification approaches assessed.

Of 4524 treatment-naïve patients with pulmonary hypertension who underwent maximal exercise testing 1,847 patients had pulmonary arterial hypertension. A step-wise reduction in one-year-mortality was seen between levels 1 (≤30m; 32% mortality) and 7 (340-420m; 1% mortality) with no mortality for levels 8-12 (≥430m) in idiopathic and connective tissue disease related pulmonary arterial hypertension. Thresholds derived at baseline of ≤180m (>10%; high-risk), 190-330m (5-10%; intermediate-risk) and ≥340m (<5%; low-risk of one-year mortality) were applied at follow-up and also accurately identified levels of risk. Thresholds were incorporated into the REVEAL 2.0 risk score calculator and French low-risk approach to risk stratification and distinct categories of risk remained. An improvement of >10% independently predicted survival, when adjusting for baseline and follow-up distance.

We have demonstrated that maximal exercise testing used in pulmonary arterial hypertension stratifies mortality-risk at baseline and follow-up. Unlike sub-maximal field walking tests, such as the 6-minute walk, improvements in exercise capacity predict outcome. This study highlights the value of maximal exercise testing in patients with pulmonary arterial hypertension.

6.2 Introduction

Pulmonary arterial hypertension (PAH) is a life-shortening condition and risk stratification is recommended to guide treatment decisions. Exercise limitation is an early presenting symptom in PAH and measures of exercise capacity are typically severely reduced (25, 220). Exercise testing is recommended as part of a multi-parameter assessment in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) and REVEAL 2.0 risk scores, and has been frequently used as an end-point in clinical trials (43, 221).

The six-minute walking test (6MWT) is the most widely used exercise test in pulmonary hypertension, and is inexpensive and simple to perform (117, 118). Absolute 6MWT distance (6MWD) correlates with haemodynamic parameters in idiopathic pulmonary arterial hypertension (IPAH) and predicts survival at baseline and follow-up (44, 222-224). Nonetheless there are concerns about a ceiling effect above a distance of 450m, and younger patients with severe disease may walk beyond 500m (116, 225-227). In addition, improvement of 6MWD in response to treatment has not been found to be independently prognostic in PAH (85, 227). Cardiopulmonary exercise testing (CPET) is a maximal test and provides comprehensive evaluation of multi-organ response to physical effort. Parameters from CPET are associated with prognosis in PAH but its utility in routine clinical practice may be limited by cost, complexity and duration of procedure (120).

The incremental shuttle walking test (ISWT) is an alternative maximal test for assessing patients with PAH, and is used in other forms of cardiac and respiratory disease (110-112). Previous studies have demonstrated correlation between ISWT distance (ISWD) and haemodynamic parameters at right heart catheterisation (RHC), and have confirmed that baseline and follow-up distances predict survival in PAH (115). The ISWT has potential advantages over the 6MWT in that it does not suffer from a ceiling effect, potentially allowing better assessment in patients who are younger or have less severe disease (115, 228). No thresholds exist for the ISWT as a risk stratification tool in PAH; the aim of this study was to assess whether thresholds could be identified and implemented into widely-used risk stratification scores.

6.3 Methods

Patients were identified from the ASPIRE (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre) registry, diagnosed with pulmonary hypertension between 1st February 2001 and 31st May 2018. Patients underwent multi-modality assessment as previously described (94). Data were collected prospectively and patients were required to have an ISWT performed at time of PH diagnosis, prior to commencement of PAH therapy. Patients with idiopathic, drug and heritable PAH were grouped and referred to as IPAH. Thresholds for low, intermediate and high-risk of one-year mortality were defined as <5%, 5-10% and >10%, respectively, and were identified in incident, treatment-naïve patients based on one-year mortality for each level. Thresholds were evaluated at follow-up, defined as the first reassessment beyond 90 days after commencing treatment. The outcome event included patients who underwent lung transplantation.

Incremental Shuttle Walking Test

The ISWT was undertaken as described by Singh *et al* (168), and as part of the standard patient evaluation. Patients complete a 10m length keeping in time to an external audible signal. Level one consists of 3 lengths (30m) and each subsequent level adds one extra length to the preceding level. The initial speed is a slow walk, 0.50m/s, increasing incrementally every level to a maximum of 2.37m/s at level 12. Each level takes one minute to complete and the test finishes at the end of level 12, a distance of 1020m. The patient continues until they are too breathless or unable to keep up with the required pace (see Table 17 for details of walking speeds). Patients unable to complete one shuttle length without oxygen were assigned an ISWD of 0m.

Mortality Data

Mortality data were obtained from the nationally-reported NHS Personal Demographics Service, updated when a death is registered in the UK, and transplant data were obtained from local databases. Patients who emigrated (n=3) were excluded from the study, as were patients not linked to a record on the Personal Demographics Service (n=2). The outcome assessed was transplant-free survival and census date was 31st May 2019, providing at least one-year of follow-up for all patients.

Statistical Analysis

Statistical analysis was performed using SPSS v25 (IBM, Chicago) and GraphPad Prism v8. Continuous data were displayed as either mean ±SD or median (first quartile, third quartile) for non-parametric data. Demographics were compared using paired and unpaired T-test for parametric data, and Wilcoxon signed-rank and Mann-Whitney U-tests for non-parametric data. Frequencies were compared using X^2. Multivariate Cox regression analysis was performed in a forward direction on all parameters with a *p* value <0.2 at univariate analysis. For all other statistical tests, a *p* value of <0.05 was considered significant. Kaplan-Meier survival curves were compared using log rank X^2. From receiver operating characteristic (ROC) analysis, a c-statistic was produced to compare variations on risk scores. Where ISWT levels demonstrated one-year mortality of 0%, these levels were combined for Kaplan Meier analysis and correlation with haemodynamics.

Ethics

Approval by the relevant ethics committee was sought and gained (STH14169, NHS Research Ethics Committee 16/YH/0352), and written consent was waived.

6.4 Results

A total of 4524 treatment-naïve patients with pulmonary hypertension, who had undergone ISWT at the time of diagnosis, were identified from the ASPIRE registry. Baseline characteristics for different forms of pulmonary hypertension are displayed in Table 18. Of these, 1240 had either IPAH or PAH related to connective tissue disease (PAH-CTD; Table 19). Kaplan Meier analysis for ISWD in all forms of PH and for IPAH/PAH-CTD at baseline are displayed in Figure 25.

IPAH and PAH-CTD

Incident, treatment naive patients with IPAH (n=603) had significant disease at right heart catheterisation, with a mean mPAP 53mmHg, pulmonary vascular resistance (PVR) 11.5 WU and cardiac index 2.3 l/min/m^2. Patients with PAH-CTD (n=637) had a mean mPAP 44mmHg, PVR 8.9 WU and cardiac index 2.6 l/min/m^2. The majority of patients received either combination oral treatment or treatment including a prostanoid.

Within one-year of diagnosis, 197 patients (15.4%) with IPAH and PAH-CTD had died or undergone transplantation. Levels of the ISWT demonstrated an inverse relationship with risk of one-year mortality (Table 17). Patients who walked 0-30m had a one-year mortality of 32%. A step-wise

reduction in percentage-mortality was seen at each level until a distance of ≥430m where there was a 0% mortality. Assignment of risk categories required concordance for both IPAH and PAH-CTD (Table 17). A high-risk of one-year mortality (>10%) was therefore defined as a distance of ≤180m, low-risk (<5%) as an ISWD ≥340m and intermediate-risk 190-330m. Corresponding values for pulmonary haemodynamic and cardiac MRI parameters are displayed in Table 20.

At follow-up ISWT the thresholds accurately identified patients at low, intermediate and high-risk in the combined IPAH and PAH-CTD cohort (one-year survival 97%, 94%, 78%, respectively), and in the individual disease groups. Kaplan Meier graphs showing five-year transplant-free survival at baseline, follow-up and demonstrating risk transition are displayed in Figure 26.

Age <50 years

Using the above thresholds in incident patients aged <50, 30% were identified as low-risk and had 0% one-year mortality. Seventy patients (28%) were intermediate risk where observed one-year mortality was underestimated at 3%, whereas 42% of patients were high-risk and had a one-year mortality of 15%. A scatterplot showing baseline and follow-up distances and one-year mortality is shown in the online data supplement (Figure 27).

Table 17: Levels of the ISWT and mortality per level for patients with IPAH and PAH-CTD

			n (%)	one-year mortality (%)		
ISWT Level*	**Distance**	**Speed (m/s)**	**IPAH & PAH-CTD**	**IPAH & PAH-CTD**	**IPAH**	**PAH-CTD**
Level 1	0-30m	0.50	267 (22)	31.8	23.4	40.8
Level 2	40-70m	0.67	206 (17)	18.5	11.0	24.3
Level 3	80-120m	0.84	196 (16)	15.3	12.4	17.8
Level 4	130-180m	1.01	172 (14)	14.5	15.2	14.2
Level 5	190-250m	1.18	137 (11)	9.5	4.5	14.1
Level 6	260-330m	1.35	110 (9)	4.5	5.5	3.6
Level 7	340-420m	1.52	69 (6)	1.4	2.3	0
Level 8	430-520m	1.69	52 (4)	0	0	0
Level 9	530-630m	1.86	18 (2)	0	0	0
Level 10	640-750m	2.03	9 (1)	0	0	0
Level 11	760-880m	2.20	2 (0)	0	0	-
Level 12	890-1020m	2.37	2 (0)	0	0	-

*Each level has a duration of one minute. Abbreviations: ISWT = incremental shuttle walking test; IPAH = idiopathic pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension related to connective tissue disease; ISWD = incremental shuttle walking distance.

Table 18: Baseline demographics in all forms of pulmonary hypertension

	All PH	PAH	PH-LHD	PH-Lung	CTEPH	Group 5
n=	4524	1847	988	766	791	129
Female (%)	61	69	66	46	50	60
Age	67 (56, 75)	63 (49, 71)	74 (67, 78)	68 (62, 75)	65 53, 74)	62 (50, 70)
WHO FC I (%)	1	1	1	0	1	3
WHO FC II (%)	19	18	24	12	22	10
WHO FC III (%)	62	63	66	55	64	63
WHO FC IV (%)	18	19	9	33	13	23
BMI	28 (24, 33)	27 (23, 32)	30 (26, 35)	27 (24, 33)	28 (25, 33)	26 (22, 32)
mRAP (mmHg)	10 (7, 15)	9 (6, 14)	14 (11, 18)	9 (6, 13)	10 (7, 14)	10 (6, 14)
mPAP (mmHg)	44 (35, 52)	47 (37, 55)	38 (32, 46)	41 (33, 49)	46 (37, 53)	45 (35, 52)
PAWP (mmHg)	12 (9, 17)	11 (8, 14)	22 (19, 26)	12 (9, 15)	12 (9, 14)	12 (9, 14)
PVR (WU)	6.2 (3.5, 10.3)	8.0 (4.8, 12.0)	3.0 (2.1, 4.7)	5.7 (3.4, 9.2)	7.3 (4.4, 11.1)	6.8 (4.3, 9.8)
SvO2 %	65 (58, 70)	65 (57, 71)	66 (60, 70)	66 (60, 71)	62 (57, 68)	63 (56, 71)
Cardiac Output (l/min)	4.6 (3.6, 5.9)	4.5 (3.4, 5.6)	5.0 (4.1, 6.1)	5.0 (3.8, 6.4)	4.5 (3.5, 5.7)	4.7 (3.9, 6.2)
Cardiac Index (l/min/m²)	2.6 (2.0, 3.1)	2.5 (1.9, 3.2)	2.7 (2.3, 3.2)	2.7 (2.1, 3.4)	2.3 (1.9, 2.8)	2.7 (2.1, 3.3)
ISWD (m)	120 (40, 220)	130 (50, 250)	120 (40, 200)	80 (30, 150)	160 (60, 290)	90 (40, 195)
Treatment (%)						
None or CCB	40	8	96	65	19	28
Oral monotherapy	34	38	4	29	68	38
Combo oral	17	36	0	5	7	23
Prostanoid +/- oral	9	18	0	2	5	12

Continuous data were non-parametric and are presented as median (1st quartile, 3rd quartile).

Abbreviations: PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; PH-LHD = pulmonary hypertension due to left heart disease; PH-Lung = pulmonary hypertension due to lung disease; CTEPH = chronic thromboembolic pulmonary hypertension; WHO FC = World Health Organisation Functional Class; BMI = body mass index; mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; SvO2 = mixed venous oxygen saturations; ISWD = incremental shuttle walking test distance; CCB = calcium channel blocker

Table 19: Baseline demographics in patients with IPAH and PAH-CTD

	IPAH & PAH CTD	**IPAH**	**PAH-CTD**
n=	1240	603	637
Female (%)	71	61	80
Age	64 (53, 72)	62 (47, 72)	66 (57, 73)
WHO FC I (%)	0	0	0
WHO FC II (%)	13	13	13
WHO FC III (%)	63	59	67
WHO FC IV (%)	23	27	19
BMI (kg/m^2)	27 (23, 31)	28 (24, 33)	26 (22, 30)
mRAP (mmHg)	9 (6, 14)	11 (7, 15)	8 (5, 12)
mPAP (mmHg)	48 (40, 56)	52 (46, 60)	43 (34, 51)
PAWP (mmHg)	10 (8, 13)	11 (8, 13)	10 (7, 12)
PVR (WU)	9.1 (5.7, 13.2)	10.5 (7.8, 14.5)	7.3 (4.7, 11.7)
SvO2 %	63 (56, 69)	61 (55, 67)	65 (58, 71)
Cardiac Output (l/min)	4.3 (3.2, 5.1)	4.0 (3.2, 5.0)	4.4 (3.4, 5.3)
Cardiac Index (l/min/m^2)	2.4 (1.9, 2.9)	2.2 (1.8, 2.7)	2.6 (2.0, 3.1)
ISWD (m)	110 (40-220)	120 (40-260)	100 (40-195)
Treatment (%)			
None or CCB	2	3	1
Oral mono	33	27	38
Combo oral	42	43	41
Prostanoid +/- oral	23	27	20

Continuous data were non-parametric and are presented as median (1st quartile, 3rd quartile).

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension related to connective tissue disease; WHO FC = World Health Organisation Functional Class; BMI = body mass index; mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; SvO2 = mixed venous oxygen saturations; ISWD = incremental shuttle walking test distance; CCB = calcium channel blockers.

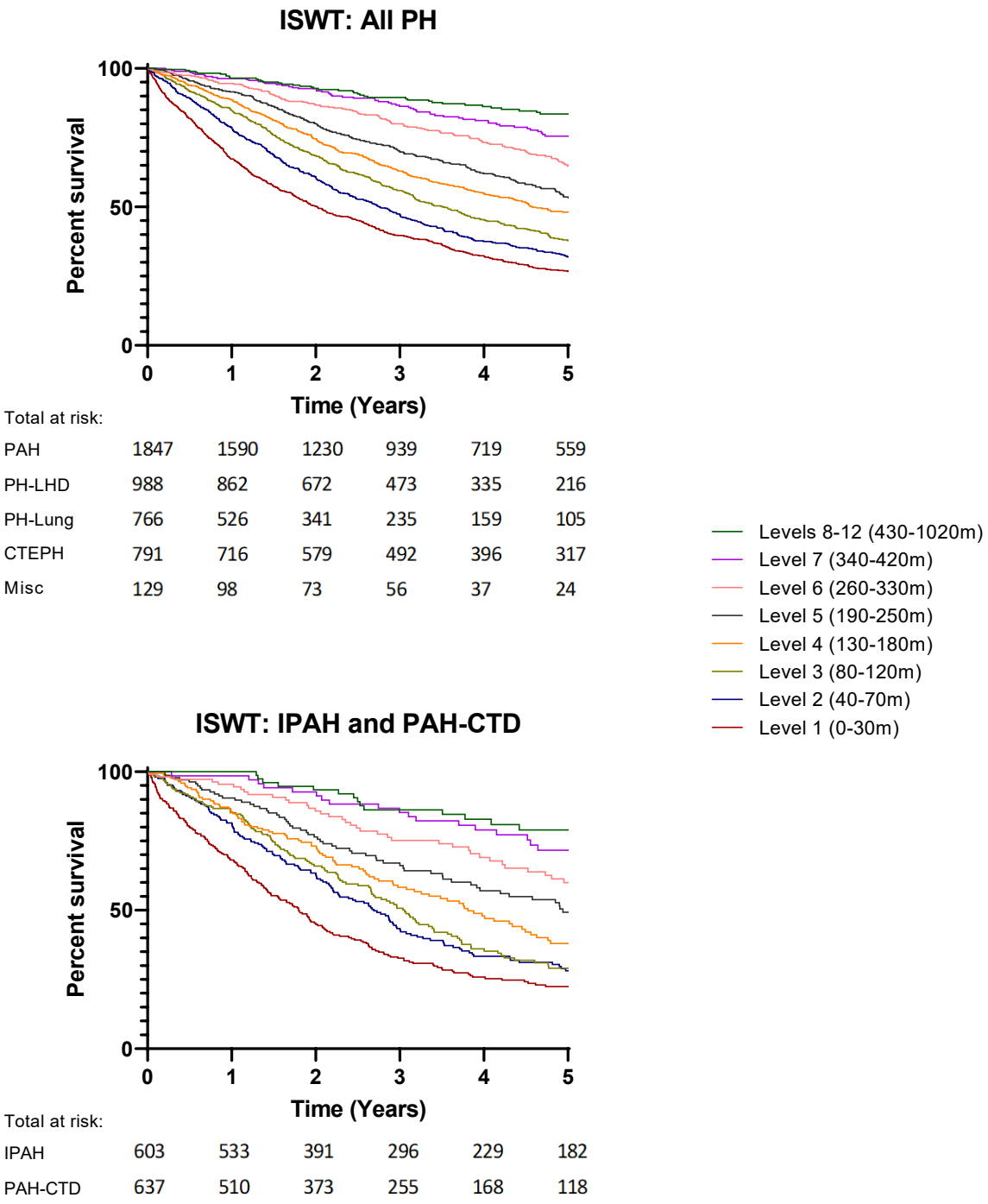

Figure 25: Kaplan Meier survival curves for a) ISWD in all PH; b) ISWD in IPAH and PAH-CTD

Abbreviations: ISWT = incremental shuttle walking test; ISWD = ISWT distance; PH = pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension due to connective tissue disease

Table 20: Association between ISWT level and haemodynamic and cardiac MRI parameters

ISWT level	n	WHO FC	mRAP (mmHg)	CI (l/min/m^2)	SvO2 (%)	RVEF (%)	RVESVi (%pred)
1	267	3.6 ±0.5	12 (8,16)	2.04 (1.67, 2.65)	58 (52, 66)	33 (27-42)	283 (225, 405)
2	206	3.3 ±0.5	10 (6, 15)	2.31 (1.80, 2.86)	61 (54, 67)	32 (25-44)	277 (163, 338)
3	196	3.1 ±0.5	10 (6, 14)	2.28 (1.81, 2.90)	62 (55, 69)	35 (24, 48)	253 (159, 371)
4	172	3.0 ±0.4	9 (6, 13)	2.40 (1.89, 2.9)	64 (58, 68)	35 (28, 43)	240 (162, 328)
5	137	2.9 ±0.5	8 (6, 13)	2.50 (2.00, 3.05)	66 (59. 70)	34 (25, 44)	237 (152, 328)
6	110	2.7 ±0.5	8 (5, 11)	2.60 (2.17, 3.20)	68 (63, 71)	36 (25, 48)	176 (132, 264)
7	69	2.6 ±0.5	9 (6, 12)	2.56 (2.20, 3.17)	66 (59, 71)	42 (34, 50)	183 (122, 258)
8-12	83	2.4 ±0.5	7 (5, 9)	2.85 (2.22, 3.22)	69 (63, 72)	40 (27, 48)	159 (120, 241)

Data are displayed as mean ±SD or median (first quartile, third quartile)

Abbreviations: ISWT = incremental shuttle walking test; MRI = magnetic resonance imaging; WHO FC = World Health Organisation Functional Class; mRAP = mean right atrial pressure; CI = cardiac index; SvO2 = mixed venous oxygen saturations; RVESVi %pred = right ventricular end systolic volume, indexed for body surface area and corrected for age and sex

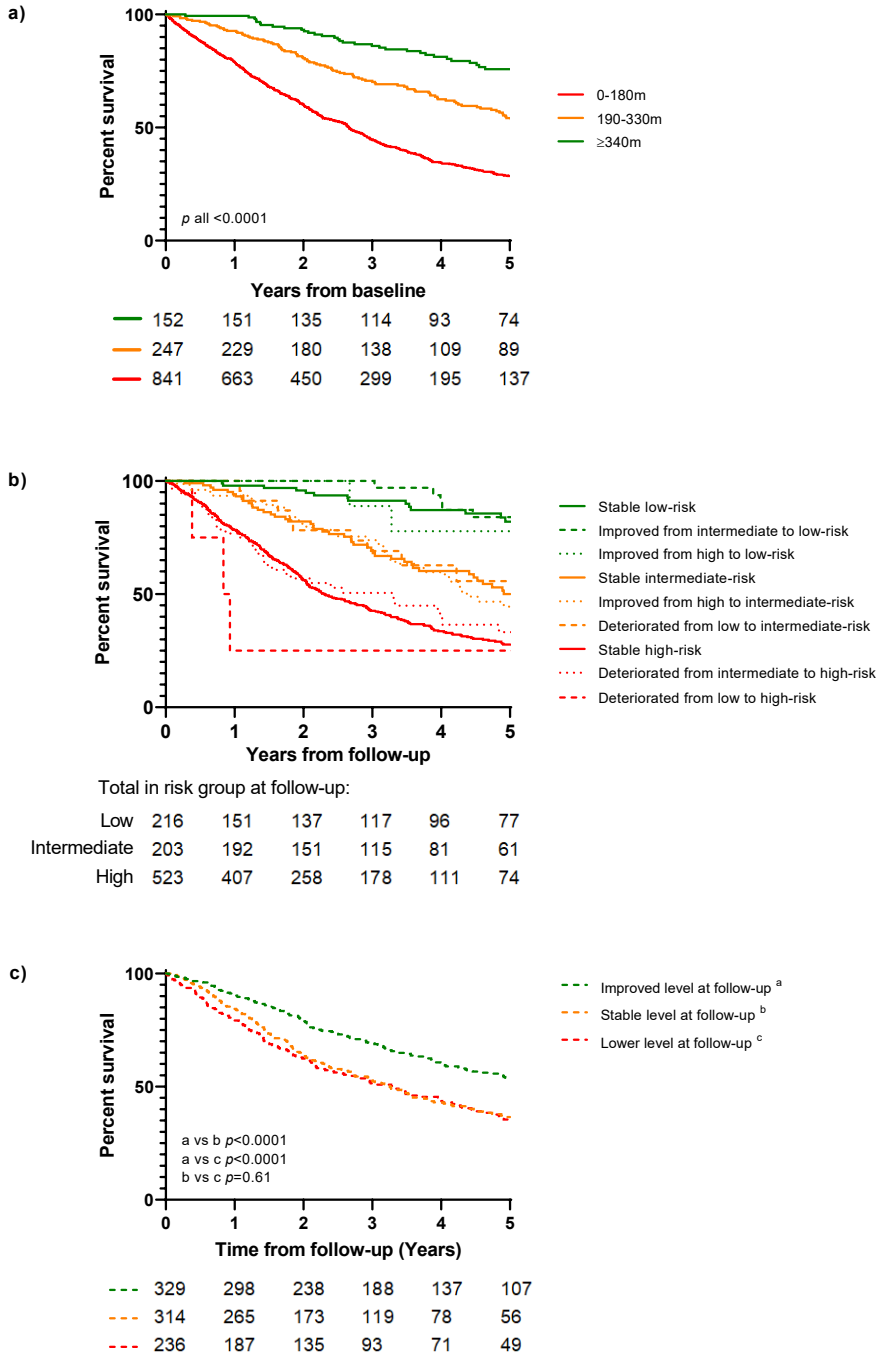

Figure 26: Kaplan Meier survival curves for ISWT: a) ISWD risk groups at baseline; b) transition of ISWD risk groups between baseline and follow-up; c) comparison of patients who, at follow-up, achieved at-least one higher ISWT level, achieved the same ISWT level, or achieved a lower level than at baseline.

Abbreviations: ISWT = incremental shuttle walking test, ISWD = incremental shuttle walking test distance

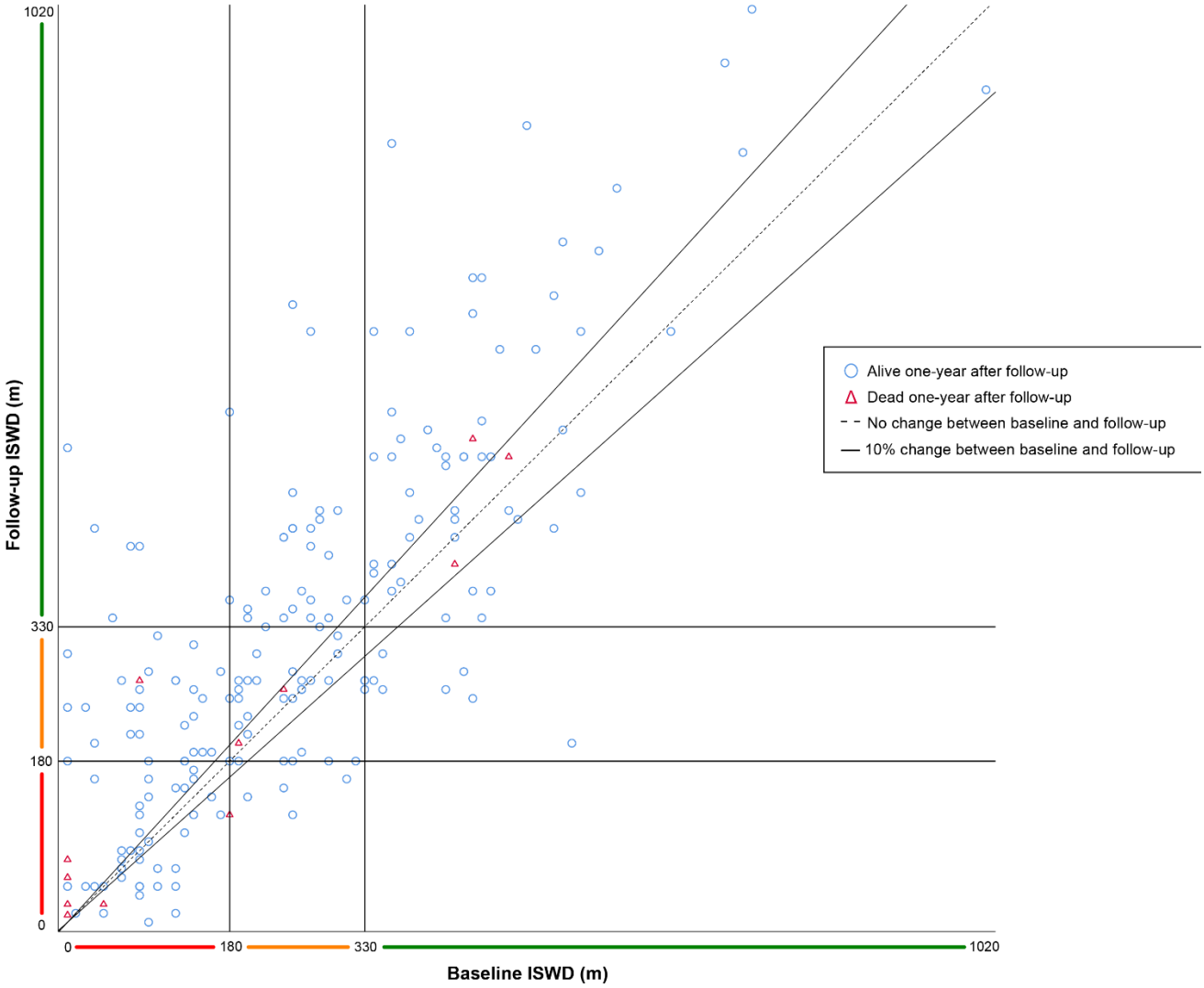

Figure 27: A scatterplot showing individual baseline and follow-up ISWT distances, and mortality or transplant within one-year of follow-up ISWDin patients aged <50 with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension due to connective tissue disease Abbreviations: ISWT = incremental shuttle walking test, ISWD = incremental shuttle walking test distance

Treatment response

Baseline median ISWD was 110m (40, 220) and paired tests at follow-up were available for 879 patients. At follow-up, 132 (15%) patients had improved their ISWT risk-category (i.e. had improved to either intermediate or low-risk distance) and 83 (9%) had deteriorated. A scatterplot demonstrating individual baseline and follow-up distance is displayed in Figure 28. At paired testing, a median improvement of +10m (-30, +50; p<0.0001) was seen overall. Patients who achieved at least one ISWT level higher than at baseline (n=329, 37%), and therefore achieved a higher velocity, had significantly better 1 and 5-year survival (90% and 54%, respectively) than those who either remained in the same level (n=314, 36%; 1 and 5-year survival 84% and 37%; p<0.0001) or deteriorated (n=236, 27%; 1 and 5-year survival 79% and 36%; p<0.0001), while there was no significant survival difference between those who were stable or deteriorated (p=0.61; Figure 26). When adjusting for baseline and follow-up ISWD, an improvement of >10% in ISWD was an independent predictor of survival (scaled HR 0.754; p<0.05) at multivariate analysis.

Use in conjunction with risk stratification scores

Patients with baseline RHC data available including mean right atrial pressure (mRAP) and cardiac index (n=1076) were selected to assess whether ISWD thresholds could be used in conjunction with other risk stratification scores, in place of 6MWD thresholds. For the FPHR low-risk invasive approach to the ESC/ERS guidelines, a low-risk 6MWD of >440m was substituted with a low-risk ISWD of ≥340m. Survival differed significantly based on the number of low-risk criteria (0-4) between all groups (p<0.05) and at ROC analysis produced a c-statistic of 0.61 (95% CI 0.57-0.66), which was unchanged when used in the IPAH group in isolation, and higher than when the FPHR approach was used without any walking test (c-statistic 0.59; 95% CI 0.55-0.64). Kaplan Meier analysis for an abbreviated three-category risk score (3 or 4 criteria = low-risk, 1 or 2 criteria = intermediate-risk, 0 criteria = high-risk) is displayed in Figure 29a, demonstrating separation of curves for each risk category (p all <0.0001). Using this three-category FPHR risk score, low and high-risk groups were accurately identified (one-year survival 96% and 78%, respectively) but risk in the intermediate group was underestimated (one-year survival 87%).

When assessing the REVEAL 2.0 score in the same population, three variations for substituting 6MWD with ISWD were derived based on i) thresholds similar to the 6MWD thresholds used in REVEAL 2.0; ii) thresholds of low, intermediate and-high risk identified at baseline; and iii) thresholds of low, intermediate and-high risk identified at baseline with an extra point addition or deduction for very-

high (≤30m) and very-low risk (≥430m), respectively, derived from baseline data shown in Table 17. The REVEAL 2.0 c-statistic for one-year mortality without a walking test was 0.66 (95% CI 0.62-0.70); including ISWD thresholds from variation iii produced a c-statistic of 0.71 (95% CI 0.67-0.75), compared to 0.69 for variations i and ii. Low (≤6), intermediate (7-8) and high-risk (≥9) REVEAL 2.0 scores (scores grouped as previously described (138)) accurately predicted one-year mortality; survival curves are displayed in Figure 29, and detailed analysis of one-year mortality for REVEAL 2.0 scores are displayed in Figure 30. In all variations, patients with a REVEAL 2.0 score ≤6 had a 0% one-year mortality, and patients with a REVEAL 2.0 score of ≥9 had a one-year mortality of 19-20%.

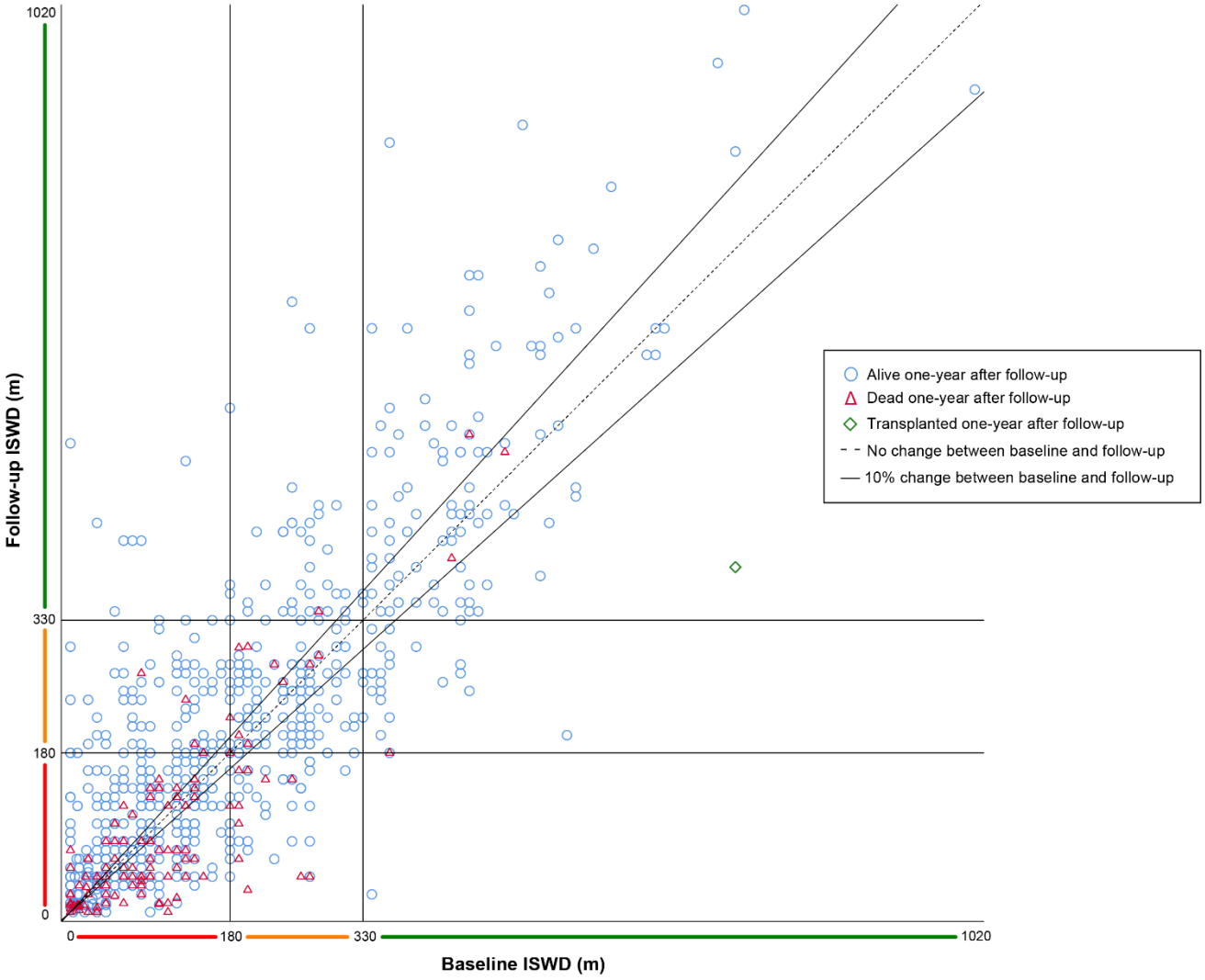

Figure 28: A scatterplot showing individual baseline and follow-up ISWT distances, and mortality or transplant within one-year of follow-up ISWD in patients with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension due to connective tissue disease (n=879).

Abbreviations: ISWD = incremental shuttle walking test distance

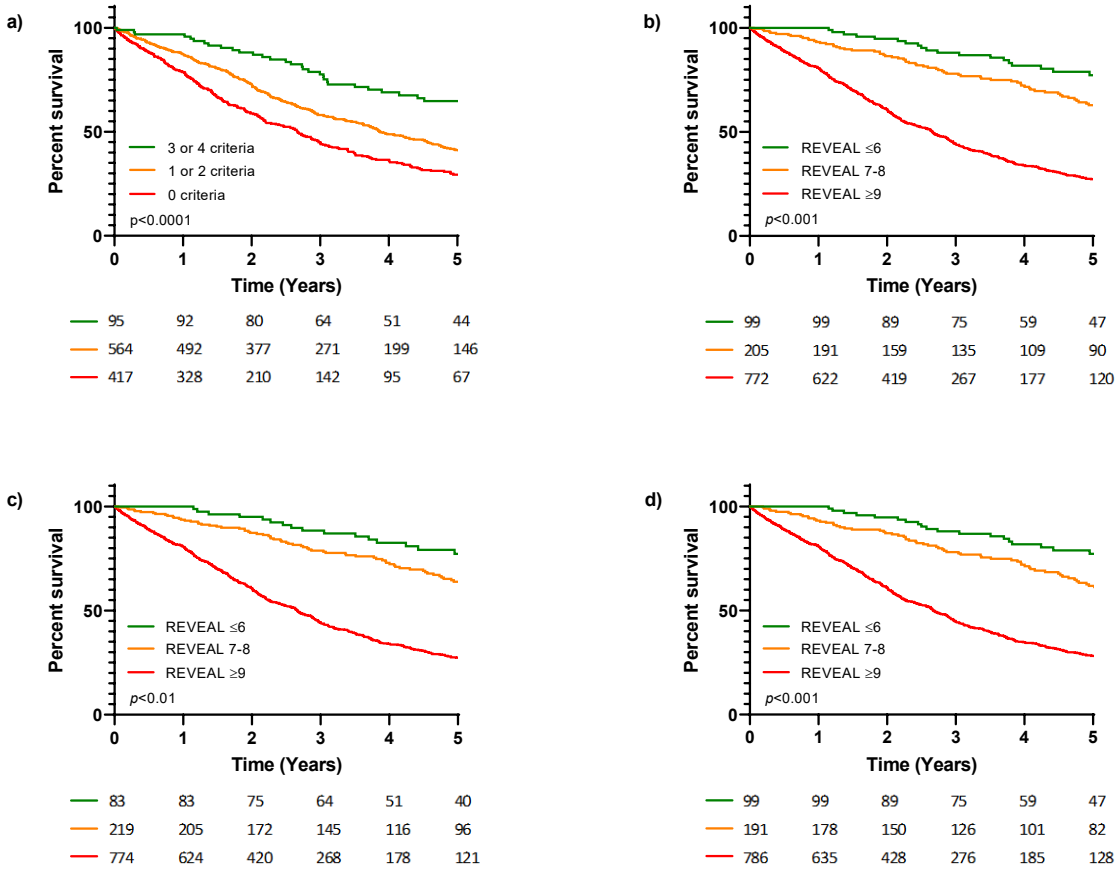

Figure 29: Kaplan Meier analysis demonstrating survival in risk stratification approaches:

a) FPHR low-risk approach;

b) REVEAL 2.0 variation i (ISWD 0-180m = +1; 190-330m = 0; 340-420m = -1; ≥430m = -2 points);

c) REVEAL 2.0 variation ii (ISWD 0-180m = +1; 190-330m = 0; ≥340m = -1 point);

d) REVEAL 2.0 variation iii (ISWD 0-30m = +2; 40-180m = +1; 190-330m = 0, 340-420m = -1; ≥430m = -2 points)

Abbreviations: REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management, FPHR = French Pulmonary Hypertension Registry, ISWD = incremental shuttle walking test distance

	Variation i		Variation ii		Variation iii	
	n (%)	1y mortality (%)	n (%)	1y mortality (%)	n (%)	1y mortality (%)
REVEAL ≤6	99 (9)	0	83 (8)	0	99 (9)	0
REVEAL 7	65 (6)	3	70 (7)	3	64 (6)	3
REVEAL 8	140 (13)	9	149 (14)	8	127 (12)	9
REVEAL 9	174 (16)	12	175 (16)	12	166 (15)	11
REVEAL 10	225 (21)	18	226 (21)	18	186 (17)	15
REVEAL 11	161 (15)	19	161 (15)	19	174 (16)	18
REVEAL ≥12	212 (20)	28	212 (20)	27	260 (24)	29

Figure 30: Risk of mortality by REVEAL 2.0 score, using variations of REVEAL 2.0 incorporating ISWD as follows:

REVEAL 2.0 variation i (ISWD 0-180m = +1; 190-330m = 0; 340-420m = -1; ≥430m = -2 points);

REVEAL 2.0 variation ii (ISWD 0-180m = +1; 190-330m = 0; ≥340 = -1 point);

REVEAL 2.0 variation iii (ISWD 0-30 = +2; 40-180m = +1; 190-330m = 0, 340-420m = -1; ≥430m = -2 points)

Abbreviations: REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; ISWD = incremental shuttle walking test distance

6.5 Discussion

In a large cohort of patients with IPAH and PAH-CTD we have demonstrated that routine use of maximal exercise testing can risk stratify patients into low, intermediate and-high risk of one-year mortality/lung transplantation. We have identified ISWT thresholds at baseline, shown the clinical utility in conjunction with other risks stratification scores and demonstrated that thresholds identified at baseline risk-stratify patients at follow-up. Unlike in sub-maximal field walking tests used in PAH, an improvement in ISWD was an independent predictor of survival.

Exercise capacity is recognised as an important physiological marker in PAH, and as a validated measure, the 6MWT has been the mainstay of exercise testing in PAH both in routine practice and in clinical trials (224). In early studies assessing PAH therapies, 6MWD was demonstrated to be a marker of treatment response (86). Absolute distances are prognostic, and deterioration of 6MWD is strongly associated with poor prognosis (85, 109). Despite this there has been criticism of the 6MWT, particularly over its role as an endpoint in clinical trials (227, 229), as prospective and retrospective studies have been unable to demonstrate that improvements in 6MWD are independently associated with survival (85, 109). Furthermore, it is a submaximal test and may suffer from a ceiling effect, potentially limiting its use in younger patients or those with mild disease (230).

We have previously shown that, as an alternative but maximal field walking test, the ISWT provides a measure of maximal exercise capacity without a ceiling effect, is sensitive to change, predicts survival and can identify exercise limitation in asymptomatic patients diagnosed with pulmonary hypertension in WHO FC I (115, 231). Using data from the present study we have now identified that maximal exercise testing using the ISWT can risk-stratify patients with IPAH and PAH-CTD. At baseline, in incident and treatment naïve patients, levels of the ISWT demonstrated good separation for both one-year and longer-term survival. As a risk stratification tool, thresholds established at baseline were applicable at follow-up. As has been demonstrated with other prognostic investigations and risk stratification tools, patients who improved their risk profile demonstrated comparable longer-term survival to patients originally displaying that level of risk (142, 206, 232).

A criticism of the 6MWT is that it suffers from a ceiling effect, whereby patients who walk >450m at baseline may not improve their walking distance in response to treatment despite improvements in WHO functional class and haemodynamics (115). In this study we have shown that, even amongst patients who walked ≥340m at baseline and remained in the low-risk group at follow-up, 63% improved absolute ISWD in response to treatment. At higher follow-up distances of ≥430m and ≥530m, 68% and 69% of patients, respectively, were able to improve their ISWD after commencing treatment. We have also demonstrated that patients who were able to achieve a higher ISWT level

had significantly better long-term survival than patients who either remained in the same level or achieved a lower level at follow-up. This is expected as each level of the ISWT requires a higher maximal walking or running velocity, which has been shown to correlate with maximal oxygen intake (peak VO_2) in other cardiorespiratory diseases (111, 112, 233). Peak VO_2 has been identified as a strongly prognostic marker of survival in PAH when measured by incremental CPET (234), and other centres have confirmed the value of incremental exercise testing in the assessment of patients with pulmonary hypertension (235). This may explain why an improvement of >10% in ISWD was an independent predictor of survival when compared to patients whose ISWD was stable, when adjusting for baseline and follow-up ISWD. While absolute distances should remain the focus of risk stratification and the goal of treatment in PAH, these data suggest that maximal exercise testing may better suited for assessing an improvement following intervention than currently used sub-maximal tests such as the 6MWT, where such an association has not been demonstrated (109). Associations between incremental exercise testing and haemodynamics have been shown previously, and we have expanded upon this by showing association between this incremental test and important prognostic parameters from cardiac MRI with a stepwise reduction in right ventricular end-systolic volume %predicted with each level of the ISWT (115, 232, 235).

Our data demonstrate that ISWT thresholds can now be considered for incorporation into widely-used risk stratification tools. Using the French low-risk invasive approach to risk stratification, substitution of the 6MWT distances with equivalent distances for low, intermediate and high-risk from the ISWT continued to show five distinct risk groups at survival analysis. When combined into a three-category risk score, patients at low (3 or 4 criteria) and high-risk (0 criteria) had a one-year mortality of 4% and 22%, respectively. Boucly *et al* note the difficulties of defining an intermediate-risk group and we found that the presence of one or two low-risk criteria underestimated one-year mortality, which was also seen when this approach was applied to the REVEAL population (138, 140). The c-statistic of 0.61 in our population of patients with IPAH is similar to that identified when the French approach was tested in the REVEAL registry (0.62), although no c-statistic is provided in the original research (138, 140).

In the REVEAL 2.0 risk score we have shown that when 6MWT distances are substituted with variations of ISWT thresholds, a three-level risk score accurately predicts one-year mortality in this population. The c-statistic of 0.71 is lower than that identified in REVEAL 2.0 (0.76), and this may be the result of a phenotypically-different PAH population. In our study we included only patients with IPAH and PAH-CTD rather than other forms of PAH such as congenital heart disease (CHD). Furthermore in our study, risk stratification approaches were applied to treatment-naïve patients rather than a mixture of incident and prevalent patients as in the REVEAL study. These factors, and particularly the absence of

patients with PAH-CHD (the presence of which scores -2 points in REVEAL 2.0) may also explain why a relatively small number of our patients were identified as being at low-risk by REVEAL 2.0 when compared to the original study and external validation studies (138, 139).

Limitations

Distances achieved at 6MWT and ISWT are not directly comparable, and the thresholds used in this study were identified from baseline data. While we have assessed and confirmed that these thresholds remain valid at follow-up, as in any single-centre study both the thresholds and their role in risk stratification tools require prospective validation in a separate population. Although we are unable to directly compare sensitivity and specificity for 6MWT and ISWT thresholds in the same population, our data support the use of the ISWT as a tool in risk stratification in PAH, and we have identified that improvements in ISWD are independently associated with survival. All-cause mortality or transplantation was used as the primary end-point, and patients may have died from causes unrelated to PAH. Finally, while the thresholds identified a large proportion of patients at high-risk of one-year mortality, this may reflect a high-risk population as demonstrated by the large number of patients with a high REVEAL 2.0 score with a corresponding one-year mortality of around 20%. Although the ISWT may be considered a more complex test it does benefit from only requiring a 10m corridor with an average time to complete the test of around 3 minutes, making it easier to incorporate into clinical practice.

6.6 Conclusion

Maximal exercise testing can be used to risk stratify patients with pulmonary hypertension including IPAH and PAH-CTD, and this study supports the routine use of maximal exercise testing in conjunction with other risk stratification tools. Unlike in sub-maximal walking tests, an improvement in maximal exercise capacity predicts outcome.

7. EmPHasis-10 health-related quality of life score predicts outcomes in patients with idiopathic and connective tissue disease-associated pulmonary arterial hypertension: results from a UK multi-centre study

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Key words: Pulmonary Arterial Hypertension, Health Related Quality of Life, Patient Reported Outcomes Measure, emPHasis-10, Risk Stratification

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7.1 Abstract

Health-related quality of life (HRQoL) scores assess symptom burden in pulmonary arterial hypertension (PAH) but data regarding their role in prognostication and risk stratification are limited. We assessed these relationships using the emPHasis-10 HRQoL measure.

1745 patients with idiopathic or connective tissue disease-associated PAH who had completed emPHasis-10 questionnaires between 2014-17 at 6 UK referral centres were identified. Correlations with exercise capacity and WHO functional class (FC) were assessed, and exploratory risk stratification thresholds were tested.

Moderate correlations were seen between emPHasis-10 scores and 6-minute walk distance (r=-0.546), incremental shuttle walking distance (r=-0.504) and WHO FC (r=0.497; *p* all <0.0001). Distribution of emPHasis-10 differed significantly between each WHO FC (*p* all <0.0001). At multivariate analysis, emPHasis-10, but not WHO FC, was an independent predictor of mortality. In a risk stratification approach, scores of 0-16, 17-33 and 34-50 identified incident patients with one-year mortality of 5%, 10% and 23%, respectively. Survival of patients in WHO FC III could be further stratified using an emPHasis-10 score ≥34 (p<0.01). At follow-up, patients with improved emPHasis-10 had improved exercise capacity (p<0.0001), and patients who transitioned risk groups demonstrated similar survival to patients originally in those risk groups.

The emPHasis-10 score is an independent prognostic marker in patients with idiopathic and connective tissue disease-associated PAH. It has utility in risk stratification in addition to currently used parameters. Improvement in emPHasis-10 score is associated with improved exercise capacity.

7.2 Introduction

Pulmonary arterial hypertension (PAH) is a rare condition, characterised by increased pulmonary vascular resistance and progressive right ventricular failure leading to premature death (9). Exertional breathlessness and limitation in physical activity are typically the earliest reported symptoms and may be caused by a number of mechanisms (203, 236). Exercise limitation may be objectively assessed by exercise testing, but limitations of day-to-day physical activity are typically assessed by healthcare professionals using the World Health Organisation (WHO) functional class.

The importance of assessing patient reported outcome measures (PROMs) in patients with pulmonary hypertension (PH) is now recognised (167, 237) and three PH-specific tools for assessing health-related quality of life (HRQoL) have been developed (196, 238, 239). One of these tools, emPHasis-10, is comprised of 10 fields (resulting in a score out of 50, where a higher score represents a higher symptom burden) which can be quickly completed by patients and is free to use and so is well suited to routine clinical use (196). The emPHasis-10 score was found to correlate strongly with measures of HRQoL, breathlessness and psychological morbidity and has high test-retest and internal consistency (196). In addition, the emPHasis-10 questionnaire has been translated into a number of other languages (240, 241). A previous single-centre study of emPHasis-10 in patients with PAH (predominantly congenital heart disease-associated) and chronic thrombo-embolic PH demonstrated prognostic significance and a correlation with WHO functional class (FC) (242). Although risk stratification has an established central role in the management of patients with PAH, PROMs are not incorporated in current risk assessment tools (43, 138, 140).

Routine HRQoL assessment using a PH-specific tool has been a mandatory field in the UK National Audit of Pulmonary Hypertension since 2014 (243). We therefore performed a multi-centre study of a large cohort of patients with idiopathic and connective tissue disease (CTD)-associated PAH to further assess the relationship between emPHasis-10 score and mortality, identify correlations with clinical parameters including exercise capacity and determine whether a threshold approach for risk stratification could be applied.

7.3 Methods

Local databases for 6 out of the 7 UK pulmonary hypertension referral centres, which together manage 94% of adult patients with a diagnosis of PAH, were interrogated (243). Patients with PAH were diagnosed as per contemporaneous international guidelines (mean pulmonary arterial pressure ≥25mmHg and pulmonary arterial wedge pressure ≤15mmHg in the absence of thromboembolic disease or conditions associated with other forms of pulmonary hypertension) (191). Anonymised demographic, haemodynamic, spirometric, exercise, emPHasis-10 and mortality data were retrieved for all patients with a diagnosis of idiopathic, drug-associated or heritable PAH (hereafter grouped as IPAH) or PAH related to CTD (PAH-CTD) with at least one recorded emPHasis-10 score between January 1st 2014 and 31st May 2018. Incident patients were required to have an emPHasis-10 score at the point of diagnosis, which was possible if diagnosed from 2014 onwards since its clinical use was introduced in the UK during that year. For prevalent patients (i.e. those diagnosed prior to 2014 or for whom no emPHasis-10 score was available at the time of diagnosis) the first available emPHasis-10 score was used. In either group, the first emPHasis-10 score was described as the baseline measurement. All patients were under regular clinical follow-up and the outcome measured was death or transplant by 31st May 2019. Follow-up data were retrieved for the first visit between 3 and 12 months after baseline emPHasis-10 score.

Statistical Analysis

Statistical analysis was performed using SPSS v26 (IBM, Chicago) and GraphPad Prism v8. Continuous data were displayed as either mean ± standard deviation, or median (first quartile, third quartile) for non-parametric data. Demographics were compared using paired and unpaired T-test for parametric data, and Wilcoxon signed-rank and Mann-Whitney U-tests for non-parametric data. Frequencies were compared using X^2. For Cox regression modelling, parameters recognised as being prognostically important were utilised: age, gender, presence of CTD (rather than IPAH), mean right atrial pressure, cardiac index and walking distance. Collinearity was assessed by measuring the variance inflation factor and tolerance between variables. EmPHasis-10 score was entered as a continuous variable in the multivariate model. Multivariate Cox regression analysis was performed in a forward direction on all parameters with a *p* value <0.2 at univariate analysis. Data were scaled to the mean and hazard ratios were based on the z-score. Two types of walking test were used (the 6-minute walking test (6MWT) and incremental shuttle walking test (ISWT)) and so for multivariate modelling, distances were converted to a z-score and combined as a single variable. For all statistical tests other than multivariate analysis, a *p* value of <0.05 was considered significant. Kaplan-Meier survival curves were

compared using log rank X^2, and were truncated at 4 years, based on the census date. Correlations were assessed using either Pearson or Spearman rank, as appropriate. Risk models were compared using the c-statistic identified from receiver operating characteristic (ROC) curve analysis. The minimal detectable change (MDC) for emPHasis-10 score was calculated using the formula: MDC = 1.96 x √2 x standard error of measurement (244).

Ethical approval was granted (IRAS 254446).

7.4 Results

A total of 1745 patients with IPAH (n=994) or PAH-CTD (n=751) who had at least one recorded emPHasis-10 score were identified. There was a female predominance (73%), and 35% of patients were incident and treatment-naïve at the time of baseline emPHasis-10 score. The median emPHasis-10 score was higher in patients with PAH-CTD (median 30 (19, 38)) than patients with IPAH (28 (17, 37)); *p*=0.001. Baseline demographics are displayed in Table 21.

Correlation with clinical parameters

Moderate correlations (*p* all <0.0001) were seen between baseline emPHasis-10 score and WHO FC (r=0.50), 6-minute walking distance (6MWD; r=-0.55) and incremental shuttle walking test distance (ISWD; r=-0.50), Table 22. In incident patients with right heart catheter data available (n=591), there were weak correlations with mean right atrial pressure (mRAP; r=0.21), cardiac index (r=-0.21) and pulmonary vascular resistance (PVR; r=0.17); *p* all <0.0001. Correlations were similar in subgroups of IPAH and PAH-CTD, apart from PVR where correlation was significant in PAH-CTD (r=0.21; *p*<0.0005) but not in IPAH (r=0.11; *p*=0.8). Correlations between WHO FC and walk distance and haemodynamics are also shown in Table 22.

Distribution of emPHasis-10 score by WHO FC at baseline is shown in Figure 31; median emPHasis-10 scores were 3, 19, 31 and 40 in WHO FC I, II, III and IV, respectively, with highly significant differences between the scores in each functional class (*p* all <0.0001).

Table 21: Patient characteristics

	All (n = 1745)	I/D/HPAH (n = 994)	PAH-CTD (n = 751)	*p* value	n
Female (%)	73	66	82	<0.0001	1745
Age at diagnosis (yrs)	59 ±17	55 ±18	64 ±13	<0.0001	1745
% incident	35	29	44	<0.0001	618
FEV_1 (%pred)	82 ±21	84 ±19	80 ±23	0.0001	1457
FVC (%pred)	92 ±23	95 ±20	89 ±27	<0.0001	1459
FEV_1/FVC	73 ±13	74 ±13	73 ±14	0.078	1459
mRAP (mmHg)	9 ±6	10 ±6	8 ±5	<0.0001	1503
mPAP (mmHg)	48 ±13	53 ±13	41 ±11	<0.0001	1573
PAWP (mmHg)	9 ±4	9 ±4	9 ±3	0.56	1496
PVR (WU)	10.5 ±5.8	12.0 ±5.7	8.7 ±5.4	<0.0001	1378
Cardiac Output (l/min)	4.2 ±1.5	4.0 ±1.5	4.3 ±1.5	<0.0005	1465
Cardiac Index (l/min/m^2)	2.4 ±0.8	2.2 ±0.8	2.5 ±0.8	<0.0001	1305
emPHasis-10	29 (18, 38)	28 (17, 37)	30 (19, 38)	0.001	1745
WHO FC I/II/III/IV (%)*	3/23/61/13	4/26/57/13	1/20/67/12		1725
6MWD*	310 (180, 408)	340 (192, 432)	241 (141, 360)	<0.0001	659
ISWD*	150 (70, 270)	160 (80, 350)	140 (60, 228)	0.001	797

**Variables were recorded at time of baseline emPHasis-10; other variables were recorded at diagnosis. Baseline 6MWD and ISWD were available in 38% and 46% of patients, respectively, with no overlap.*

Abbreviations: I/D/HPAH = idiopathic/drug/heritable pulmonary arterial hypertension, PAH-CTD = connective tissue disease related pulmonary arterial hypertension, mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; WHO FC = World Health Organisation functional class; 6MWD = six-minute walking test distance; ISWD = incremental shuttle walking test distance

Table 22: Correlation of emPHasis-10 and WHO functional class with walk distance and pulmonary haemodynamics

	6MWD (m)	**ISWD (m)**	**mRAP (mmHg)**	**CI (L/min/m^2)**	**PVR (WU)**
emPHasis-10	-0.55* (n=659)	-0.50* (n=797)	0.21* (n=575)	-0.21* (n=525)	0.17* (n=550)
WHO FC	-0.60* (n=653)	-0.59* (n=796)	0.18* (n=572)	-0.18* (n=523)	0.18* (n=548)

*Correlations assessed by Pearson or Spearman-Rank tests as appropriate. * = p<0.001.*

Abbreviations: 6MWD = 6-minute walking distance, ISWD = incremental shuttle walking distance, mRAP = mean right atrial pressure, CI = cardiac index, PVR = pulmonary vascular resistance, WHO FC = World Health Organisation functional class.

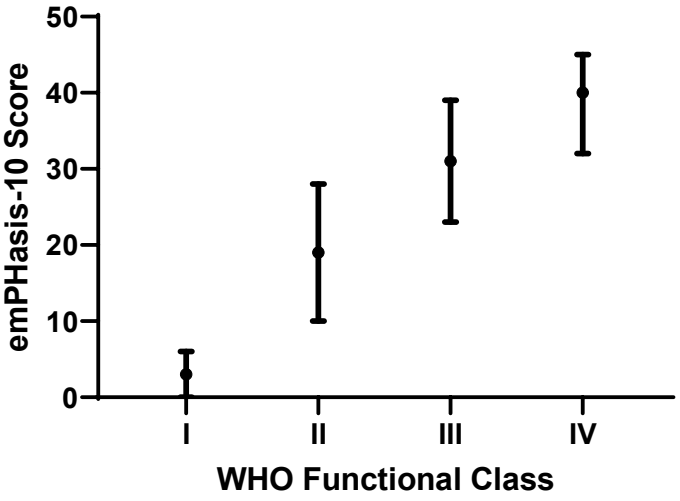

Figure 31: Distribution of emPHasis-10 score by WHO functional class at baseline

Abbreviations: WHO = World Health Organisation

Risk Stratification

During the course of the study 674 (39%) patients died, of which 240 (14%) died within one-year of baseline emPHasis-10 score; one-year mortality in incident and prevalent patients was 16% and 12%, respectively. An exploratory three-level score was developed based on a tertile group approach: scores of 0-16 were defined as low-risk, 17-33 as intermediate-risk, and 34-50 as high-risk. Using these thresholds, 22% of all patients were defined as low-risk, 41% as intermediate-risk and 37% as high-risk of one-year mortality. Survival curves for these risk groups are shown for incident patients in Figure 32a, prevalent patients in Figure 32b and for all patients in Figure 32c. In incident patients, one-year mortality for the low, intermediate and high-risk groups was 5%, 10% and 23%, respectively. In all patients, one-year mortality for the low, intermediate and high-risk groups was 4%, 12% and 21%, respectively. In all patients with IPAH, one-year mortality in low, intermediate and high-risk groups was 4%, 9% and 18%, whereas in PAH-CTD, one-year mortality was 6%, 15% and 25%, respectively. Incident patients in functional class III who were in low/intermediate emPHasis-10 risk groups (emPHasis-10 score 0-33) had superior survival than those in the high-risk group (emPHasis-10 score 34-50) with 1 and 3-year survival of 90% and 67% vs 81% and 56%; $p<0.01$; Figure 33). Very similar observations were made in functional class III patients at their first follow-up visit.

Survival Analysis

Three multivariate analysis models were developed in the incident population (Table 23). Model 1 utilised accepted prognostic parameters: age, gender, PAH-CTD rather than IPAH, WHO FC, mRAP and cardiac index. EmPHasis-10 and exercise capacity were sequentially added into models 2 and 3. Unlike WHO FC, emPHasis-10 score was an independent predictor of outcome in models 2 (scaled HR 1.565; $p<0.0001$) and 3 (scaled HR 1.226; $p<0.05$). There was no significant collinearity between parameters used in the model.

Magnitude of change

The MDC for emPHasis-10 score was calculated to be 9. Follow-up emPHasis-10 data were available for 1068 patients (61%). EmPHasis-10 score changed by at least 9 points in 33% of patients (IPAH 32%, PAH-CTD 34%) between baseline and follow-up. Thirty-seven percent of patients moved risk groups, of which 19% improved at least one risk group. In patients who moved from high-risk to intermediate or low-risk, the median change in emPHasis-10 score was -12 (-6, -19) points, and in patients who

deteriorated to high-risk the median change was +13 points (+8, +17). Patients who either improved to low or intermediate-risk, or deteriorated to high-risk demonstrated similar long-term survival to patients originally in those risk groups (Figure 32d).

At paired testing, patients who improved emPHasis-10 score by ≥ the MDC of 9 points had significantly improved walk distances at follow-up; ISWD increased by 30m (0, 90; p<0.0001, Figure 34a) while 6MWD increased by a median distance of 32m (-4, +113; p<0.005, Figure 34b). A significant fall in ISWD of -20m (-60, 0; *p*<0.0001, Figure 34a) and no significant change in 6MWD (0m (-29, +57), Figure 34b) was observed in patients whose emPHasis-10 score deteriorated by at least 9 points. In the remaining patients in whom there was a change of <9 points there was no significant change in either ISWD (0m (-30, +20)) or 6MWD (0m, (-11, +53)). The relationship between change in emPHasis-10 and change in walk distance differed depending on whether patients were incident or prevalent at the time of their baseline walk (relationship being stronger in incident patients) and whether they performed the ISWT or 6MWT (relationship being stronger in patients who performed the ISWT). In patients whose emPHasis-10 score deteriorated by ≥9 points, ISWD fell significantly in both incident and prevalent populations. In patients whose emPHasis-10 score improved ≥9 points ISWD increased significantly in incident, but not prevalent, patients (Figure 34c and Figure 34e). In patients in whom a 6MWT was performed, an improvement was observed in incident patients whose emPHasis-10 score either improved or deteriorated by ≥9 points (Figure 34d), while no significant change was seen in prevalent patients (Figure 34f).

Table 23: Univariate and multivariate analysis in incident patients

	Univariate		**Multivariate**	
Model 1	**Scaled HR**	***p* value**	**Scaled HR**	***p* value**
Age	2.063	<0.0001	2.177	<0.0001
Gender (ref. Female)	1.316	0.054		
PAH-CTD (ref. IPAH)	1.336	0.031	1.444	0.017
WHO FC III (ref I&II)	1.817	0.009		
WHO FC IV (ref I&II)	3.642	<0.0001	2.978	<0.0001
mRAP	1.196	0.006	1.227	0.005
Cardiac Index	0.756	0.001		
Model 2	**Scaled HR**	***p* value**	**Scaled HR**	***p* value**
Age	2.063	<0.0001	2.180	<0.0001
Gender (ref. Female)	1.316	0.054		
PAH-CTD (ref. IPAH)	1.336	0.031		
WHO FC III (ref I&II)	1.817	0.009		
WHO FC IV (ref I&II)	3.642	<0.0001		
mRAP	1.196	0.006		
Cardiac Index	0.756	0.001		
emPHasis-10	1.518	<0.0001	1.447	<0.0001
Model 3	**Scaled HR**	***p* value**	**Scaled HR**	***p* value**
Age	2.063	<0.0001	1.860	<0.0001
Gender (ref. Female)	1.316	0.054		
PAH-CTD (ref. IPAH)	1.336	0.031		
WHO FC III (ref I&II)	1.817	0.009		
WHO FC IV (ref I&II)	3.642	<0.0001		
mRAP	1.196	0.006		
Cardiac Index	0.756	0.001		
emPHasis-10	1.518	<0.0001	1.226	0.047
Walking distance*	0.461	<0.0001	0.574	<0.0001

**Two types of walking test were used (the 6-minute walking test and incremental shuttle walking test). For Cox regression modelling, distances were converted to a z score and combined.*

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, CTD-PAH = connective tissue disease related pulmonary arterial hypertension, WHO FC = World Health Organisation functional class; mRAP = mean right atrial pressure, HR = Hazard Ratio

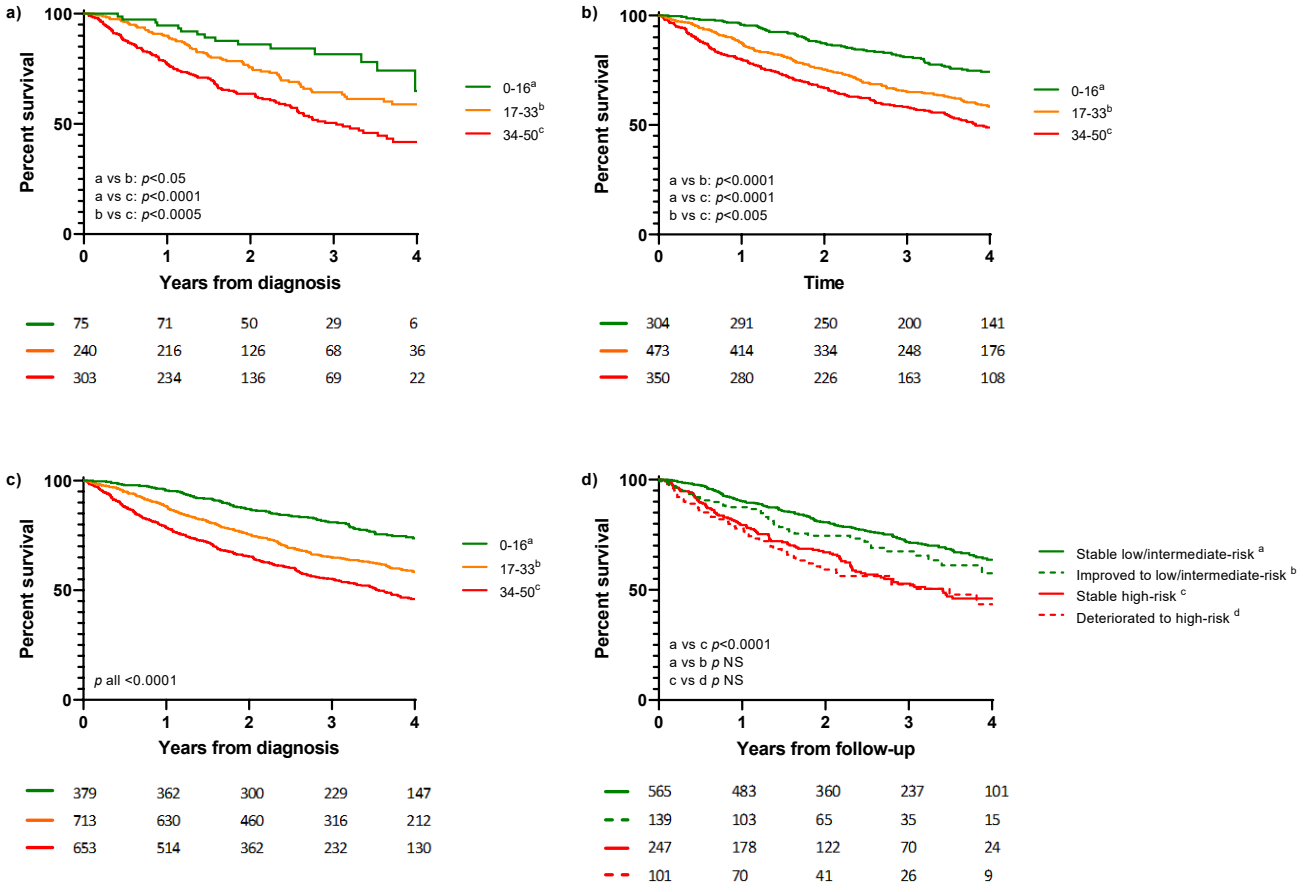

Figure 32: Kaplan Meier survival curves demonstrating survival from baseline emPHasis-10 score for a) incident patients; b) prevalent patients, c) all patients; d) risk transition in all patients between baseline and follow-up emPHasis-10 score

Abbreviations: NS = not significant

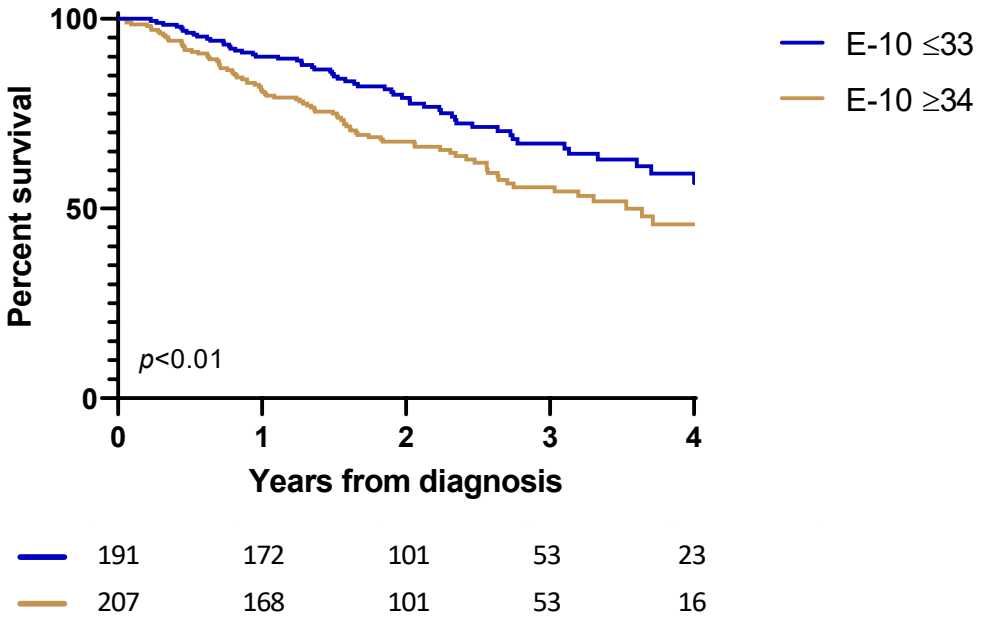

Figure 33: Survival in incident patients with WHO functional class III symptoms, dichotomised by emPHasis-10 score ≤33 or ≥34.

Abbreviations: WHO = World Health Organisation, E-10 = emPHasis-10 score

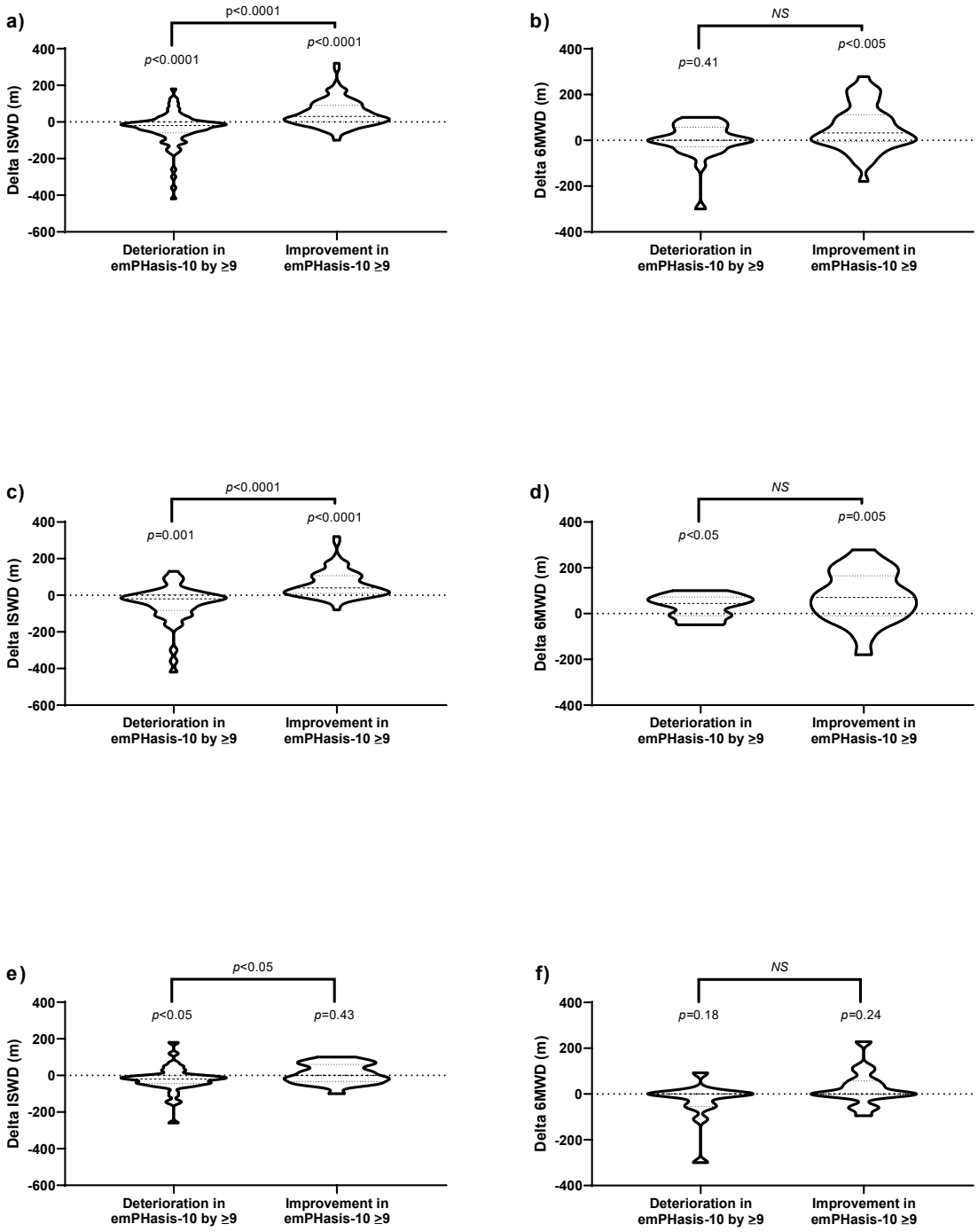

Figure 34: Change in walk distance (ISWD or 6MWD) in patients whose emPHasis-10 score deteriorated by ≥9 or improved by ≥9 between baseline and follow-up. Figure 4a & b: all patients, figure 4c & d: incident patients, figure 4e & f: prevalent patients

Abbreviations: ISWD = incremental shuttle walking test distance; 6MWD = six-minute walking test distance; E-10 = emPHasis-10. Violin plots: dashed line = median, dotted line = 25th and 75th centile

7.5 Discussion

To our knowledge, this is the largest study to assess the role of quality of life scores in patients with PAH, and in this multi-centre study we report on data from centres treating the vast majority of the adult PAH population in the UK. We have demonstrated that the emPHasis-10 score is an independent predictor of outcomes when adjusting for haemodynamics and WHO FC and also has utility in risk stratification, including within patients in WHO FC III. We have also observed moderate correlations with WHO FC and exercise capacity and weaker correlations with pulmonary haemodynamics. Furthermore, we have also demonstrated that improvement in emPHasis-10 score, as opposed to a static or worsening score, is associated with improvements in exercise capacity.

Generic (Short Form Health Survey (SF-36)), heart failure-specific (Minnesota Living with Heart Failure questionnaire), and PAH-specific (emPHasis-10 and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)) PROMs have previously been identified as having prognostic importance in PAH (242, 245-247). Correlations between CAMPHOR and SF-36 and 6-minute walking test distance have also been demonstrated (246, 248, 249). The widespread clinical use of the CAMPHOR score may, however, be limited by its length (65 fields over 3 domains: symptoms, functioning and quality of life) and lack of open access (250). A third PH-specific PROM, the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) tool, which consists of 22 fields over 2 domains (symptoms and impacts) has also been developed (239). Although PAH-SYMPACT is responsive to change, its relationship to haemodynamics and survival is not known (251).

A previous single-centre study involving 687 patients (314 PAH associated with congenital heart disease, 109 IPAH, 111 CTD-PAH and 131 chronic thromboembolic PH) assessed the relationship between emPHasis-10 and survival (242). In that study, Cox regression analysis demonstrated emPHasis-10 to be predictive of survival, independent of WHO FC, in PAH associated with congenital heart disease, but not in IPAH and CTD-PAH. In our study, which included much larger numbers of patients with IPAH and CTD-PAH, emPHasis-10 was an independent prognostic marker in IPAH and CTD-PAH, even when allowing for a number of variables known to be strongly prognostic in PAH including mRAP and cardiac index. This was not the case for WHO FC and it is interesting to note that Boucly *et al* also observed that baseline WHO FC was not an independent predictor of outcome in their paper from the French Registry (140).

In incident patients, an exploratory risk stratification approach separating emPHasis-10 scores into three bands based on an equal range of scores in each group (thresholds of ≤16, 17-33 and ≥34) identified distinct risk groups with significant survival differences (corresponding one-year mortality of 5%, 10% and 23%, respectively). These levels of one-year mortality are very similar to risk thresholds

of low (<5%), intermediate (5-10%) and high-risk (>10%) proposed by the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for risk stratification in PAH. Using these risk thresholds, we identified that patients who either improved to intermediate or low-risk, or deteriorated to high-risk at follow-up emPHasis-10 assessment had a similar longer-term survival to patients who were originally in those risk groups. This effect has been seen in a number of other risk stratification parameters and scores (142, 206, 232), and the importance of achieving specific PROM thresholds in PAH has also been observed with the generic SF-36 (252). The majority of patients are in WHO FC III at the time of diagnosis and we were therefore interested whether the emPHasis-10 score could refine these patients into higher and lower risk groups. We observed that a threshold score ≥34 was indeed able to identify functional class III patients at higher and lower risk of one-year mortality at both diagnosis and at first follow-up.

We observed moderate correlations between emPHasis-10 and exercise capacity (r=0.55 and 0.50) and WHO FC (0.50) and only weak correlations with pulmonary haemodynamics (r ranging between 0.17 and 0.21). The correlations with exercise capacity compare favourably with some reports regarding the other 2 PH-specific PROMs; Gomberg-Maitland *et al* reported weaker correlations between 6MWD and the 3 domains of CAMPHOR (symptoms r=0.35, functioning 0.45, HRQoL 0.33) in 147 PAH patients while Chin *et al* observed weak to moderate correlations between domains of the PAH-SYMPACT and 6MWD (r =-0.14 to -0.57) in 278 PAH patients (251). More recently, however, Reis *et al* observed stronger correlations between 6MWD and the 3 CAMPHOR domains (r=-0.67, -0.74 and -0.61) in 49 patients with PAH or chronic thromboembolic PH (249, 253). To date, there have been no previous reports of correlations of PH-specific PROMs and pulmonary haemodynamics. The correlations we observed were, however, comparable to those observed by Mathai *et al* between components of the SF-36 generic HRQoL tool and haemodynamics in 87 patients with PAH (although in their study, many of these correlations were non-significant) (245).

Finally, we have demonstrated that an improvement in emPHasis-10 score of at least the MDC (≥9) at follow-up was associated with an increase in exercise capacity in incident patients whereas a reduction in emPHasis-10 score by ≥9 was associated with a decrease in exercise capacity when assessed by the ISWD. The vast majority of incident patients will have been started on PAH therapies, whereas in prevalent patients there may have been no treatment change between assessments, which may partly explain the stronger relationship between change in walk distance and change in emPHasis-10 score in the incident group. The reason for the stronger relationship between change in ISWD (as opposed to 6MWD) and change in emPHasis-10 is not clear but may reflect the different nature of the tests; the ISWT is an externally-paced measure of maximal exercise capacity while the 6MWT is an internally-paced assessment of sub-maximal exercise capacity. These data suggest that emPHasis-10 is

responsive to change, however further work is needed to define the minimal clinically important difference.

Limitations

While this study was able to demonstrate important associations between emPHasis-10 score and time to death or transplantation, other measures of clinical deterioration including hospitalisation due to heart failure and escalation of therapy were unavailable. In addition, while emPHasis-10 scores were prospectively collected, this was a retrospective study and there were some data availability issues. Treatment data were not available; it is possible that PAH-specific therapies may affect HRQoL both negatively, in terms of side effects and the effects of complex treatments on lifestyle, but also positively, in terms of improvements in right ventricular function translating into amelioration of symptoms. Finally, data regarding comorbidities, such as the presence and extent of parenchymal lung disease in patients with PAH-CTD, were unavailable. Assuming that comorbidities such as lung disease adversely affect HRQoL the inclusion of patients with parenchymal lung disease would likely weaken the relationships between emPHasis-10 and functional parameters, treatment response and survival.

7.6 Conclusion

The emPHasis-10 score correlates with WHO FC, exercise capacity and haemodynamics and is an independent prognostic marker in patients with IPAH and PAH-CTD. The survival of patients within WHO FC III can be further stratified using emPHasis-10 score. Improvement in emPHasis-10 is associated with improvement in exercise capacity, although further work to determine the minimal clinically important difference is required.

8. Summary and Conclusion

This thesis comprises two main sections, the first identifying important clinical phenotypes in patients with pulmonary hypertension, and the second assessing whether non-invasive investigations and tools can be used to risk stratify patients with pulmonary arterial hypertension.

In the first section, two specific phenotypes have been described. In chapter 3 patients with partial anomalous pulmonary venous drainage are discussed. Although this a rare congenital defect, identification is important as patients may require surgical correction, either for the anomalous drainage or for associated atrial septal defects. The data demonstrate that, in patients presenting with pulmonary hypertension, partial anomalous pulmonary venous drainage is frequently missed as a diagnosis prior to assessment at a specialist unit despite a majority having undergone local CT scanning. Furthermore, a large number of atrial septal defects were newly identified, despite these patients having previously undergone CT imaging. These data are supported by similar findings in other studies (179), although the data in chapter 3 represent the largest published cohort of patients with PAPVD.

Data in chapter 4 show the importance of describing and assessing the extent of lung disease in patients who are classified as having IPAH based on current recommendations. Patients with radiologically-mild parenchymal lung disease did not demonstrate an improvement in exercise capacity when treated with targeted therapy and also have significantly worse outcomes, when compared to patients who did not have any radiological evidence of lung disease. While these data require confirmation in prospective RCTs, they may have important implications for clinicians managing patients with IPAH and for investigators assessing the effect of novel PAH therapies. Exclusion criteria for these trials typically only consist of spirometric criteria, and the presence of mild lung disease would not merit exclusion. In this study, patients had relatively preserved spirometry and would not have been excluded from PAH clinical trials. From a clinician perspective these data may advocate against aggressive treatment of PAH in these patients with parenteral treatments, although given the absence of a control cohort, it is possible that patients may have had an even poorer prognosis had they not received targeted therapy. In addition, the presence of mild parenchymal lung disease is not included in any current risk stratification tools for patients with IPAH despite this significant survival disadvantage.

This study has not assessed the impact of lung disease in patients with PAH-CTD, and approximately 75% of patients with systemic sclerosis develop interstitial lung disease (254). In the presence of PH, such patients often receive targeted therapies but the clinical benefit of these therapies is unclear. Some studies in patients with PH and parenchymal lung disease have shown improvement in

haemodynamics, but a study of 70 patients with ILD in the presence of PAH-CTD did not show clear benefits from treatment (255-257). Whether the extent of lung disease is important in these patients remains unclear, and further studies assessing the role of PAH targeted therapies in varying extents of lung disease in this population may be warranted.

These two studies particularly demonstrate the role that CT imaging has in establishing the correct diagnosis in patients presenting with pulmonary hypertension, but also supports previous studies highlighting that imaging can provide important prognostic information (258). The recent Pulmonary Vascular Research Institute (PVRI) statement on imaging and pulmonary hypertension recognise the important role that CT imaging has in patients presenting with pulmonary hypertension (169), and the first two studies presented in this thesis support the use of CT imaging at diagnosis, although its use as a routine risk stratification tool at follow-up is limited by ionising radiation exposure.

The second part of this thesis focuses on risk stratification using non-invasive investigations and assessments. While thresholds have been proposed for a number of other non-invasive investigations such as the 6-minute walking test and BNP/NT-proBNP, no thresholds have previously been proposed for volumetric measurements taken at cardiac MRI, which has been established as the gold standard marker of right ventricular function and is recognised as a prognostic tool in PAH (160). In contrast to CT imaging, cardiac MRI is particularly attractive as a non-invasive risk-stratification tool as it does not involve radiation exposure, whilst also providing cine images allowing visual assessment of the cardiac chambers and facilitating volumetric measurements. Using discovery and test cohorts, thresholds have been identified that could be incorporated into clinical use. Both right ventricular ejection fraction (RVEF) and percent-predicted right ventricular end systolic volume index (RVESVi %pred) were found to be prognostic at baseline and follow-up. A large proportion of patients at low-risk of one-year mortality were identified using RVESVi %pred and this was therefore selected for assessment alongside the REVEAL 2.0 risk score calculator and French low-risk approach to risk stratification. In both models cardiac MRI improved risk stratification, as measured by c-statistic, and further delineated risk in patients found to be at intermediate or high risk using either of these approaches.

Exercise capacity is recognised as an important prognostic marker in PAH and is typically assessed using the sub-maximal 6-minute walking test (6MWT). Absolute distances measured using the 6MWT predict mortality. However, despite the widespread use of 6MWT as a primary endpoint in the majority of PAH clinical trials, an improvement in 6MWT distance has not been shown to be an independent predictor of mortality. In this study I hypothesised that an improvement in maximal exercise capacity, as measured by the incremental shuttle walking test, would predict outcome and have demonstrated that improvement of 10% at follow-up independently predicted improved

survival, when adjusting for baseline and follow-up distances. Cardiopulmonary exercise testing is recognised as the gold standard measure of exercise capacity, and this study highlights the importance of maximal exercise testing in patients with PAH. Compared to the incremental shuttle walking test, cardiopulmonary exercise testing is time-consuming and expensive but does provide a more comprehensive evaluation of multi-organ response to physical effort.

Whilst objective measures of improvement such as cardiac MRI and exercise capacity are prognostically useful, assessing quality of life in patients with PAH is clearly important. Such measures have typically been physician-assessed using WHO functional class but increasingly the importance of patient-reported outcomes measures (PROMs) is recognised (167). Chapter 7 therefore assesses whether PROMs can be used to predict outcomes in patients with PAH and whether they have a role as a risk stratification tool. Three PAH specific PROMs exist, but only the emPHasis-10 score is in use in all UK PAH referral centres. Data for baseline and follow-up emPHasis-10 scores were therefore collected from centres representing 94% of adults receiving treatment for PAH in the UK. Using these data, the study identified that emPHasis-10 score is an important prognostic marker in PAH. The score was an independent predictor of outcomes, when adjusting for haemodynamics and WHO functional class, and has utility in risk stratification. In patients who presented in WHO functional class III, which typically represents the majority of patients diagnosed with PAH, the emPHasis-10 score was able to stratify patients into a lower and higher risk group. In addition, the study has confirmed that emPHasis-10 score correlates with WHO functional class and also shows moderate correlation with exercise capacity (242).

8.1 Limitations

Specific limitations for each study are outlined in the individual chapters. While data were prospectively collected, the main limitation of the studies included in this thesis is that they are based on retrospective data and, apart from the study presented in chapter 7, from a single centre. Nonetheless, the studies consist of large cohorts and in several cases represent the largest data that have been published in the individual areas. Given the retrospective nature of these studies, prospective validation is required. This is particularly applicable to patients with IPAH and mild lung disease where there has so far been a paucity of large prospective data from well-conducted studies aimed at determining whether targeted treatment is beneficial for these patients.

8.2 Future directions

A number of areas for potential future research have been suggested by the studies in this thesis. Whilst lung disease has been identified as a marker of poor outcomes in IPAH, its impact in other forms of PAH remains unclear. Parenchymal lung disease is frequently seen in patients with PAH-CTD, and

while small studies have assessed the benefit of therapies in selected groups, it remains unclear whether the extent of lung disease predicts response to treatment. Therefore, further work aimed at identifying which patients have specifically developed a potentially treatable vasculopathy would be beneficial.

There are emerging data showing the role of machine learning in the interpretation of CT images and lung parenchyma. Further work could compare the qualitative description of CT imaging provided in chapter 4 with a machine learning approach.

The aim of this thesis was not to develop a new risk stratification calculator for patients with PAH, as two validated tools are already in use. Nonetheless combination of investigations identified in this thesis could be considered, particularly cardiac MRI and the incremental shuttle walking test, which identify a large proportion of patients at low and high-risk of one-year mortality, respectively.

8.3 Conclusion

To conclude, non-invasive assessments can identify important phenotypes and improve risk stratification in patients with PAH and the hypothesis is therefore accepted. These studies advance our understanding of PAH and it is hoped that improved accuracy of clinical phenotyping and risk stratification may lead to an improved quality of life for individual patients.

9. Bibliography

1. Hatano S, Strasser T, Organization WH. Primary pulmonary hypertension: report on a WHO meeting, Geneva, 15-17 October 1973. 1975.
2. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Eur Respir J. 2008;32(5):1371-85.
3. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006;129(3):746-52.
4. Hoeper MM. The new definition of pulmonary hypertension. Eur Respir J. 2009;34(4):790-1.
5. Damy T, Goode KM, Kallvikbacka-Bennett A, Lewinter C, Hobkirk J, Nikitin NP, et al. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. Eur Heart J. 2010;31(18):2280-90.
6. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. 2009;53(13):1119-26.
7. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest. 1993;103(3):685-92.
8. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):25S-32S.
9. Kiely DG, Elliot CA, Sabroe I, Condliffe R. Pulmonary hypertension: diagnosis and management. BMJ. 2013;346:f2028.
10. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. American journal of respiratory and critical care medicine. 2008;177(10):1122-7.
11. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973-81.
12. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JS, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. American journal of respiratory and critical care medicine. 2012;186(8):790-6.
13. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J. 2009;34(4):888-94.
14. Humbert M, McLaughlin VV. The 4th World Symposium on Pulmonary Hypertension. Introduction. J Am Coll Cardiol. 2009;54(1 Suppl):S1-2.
15. Galiè N, Simonneau G. The Fifth World Symposium on Pulmonary Hypertension. Journal of the American College of Cardiology. 2013;62(25):D1-D3.
16. Hoeper MM. Definition, classification, and epidemiology of pulmonary arterial hypertension. Semin Respir Crit Care Med. 2009;30(4):369-75.
17. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, et al. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J. 2015;46(3):728-37.
18. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
19. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J. 2019;53(1).

20. Kovacs G, Agusti A, Barbera JA, Celli B, Criner G, Humbert M, et al. Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease. Is There a Pulmonary Vascular Phenotype? American journal of respiratory and critical care medicine. 2018;198(8):1000-11.
21. Hoeper MM, Vonk-Noordegraaf A. Is there a vanishing pulmonary capillary syndrome? Lancet Respir Med. 2017;5(9):676-8.
22. Graham BB, Bandeira AP, Morrell NW, Butrous G, Tuder RM. Schistosomiasis-associated pulmonary hypertension: pulmonary vascular disease: the global perspective. Chest. 2010;137(6 Suppl):20S-9S.
23. Koehler R, Grunig E, Pauciulo MW, Hoeper MM, Olschewski H, Wilkens H, et al. Low frequency of BMPR2 mutations in a German cohort of patients with sporadic idiopathic pulmonary arterial hypertension. J Med Genet. 2004;41(12):e127.
24. Pfarr N, Szamalek-Hoegel J, Fischer C, Hinderhofer K, Nagel C, Ehlken N, et al. Hemodynamic and clinical onset in patients with hereditary pulmonary arterial hypertension and BMPR2 mutations. Respir Res. 2011;12(1):99.
25. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. American journal of respiratory and critical care medicine. 2006;173(9):1023-30.
26. Benza RL, Gomberg-Maitland M, Miller DP, Frost A, Frantz RP, Foreman AJ, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest. 2012;141(2):354-62.
27. Souza R, Jardim C. Trends in pulmonary arterial hypertension. European respiratory review : an official journal of the European Respiratory Society. 2009;18(111):7-12.
28. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. The European Respiratory Journal. 2017;50(2):1700889.
29. Kiely DG, Lawrie A, Humbert M. Screening strategies for pulmonary arterial hypertension. Eur Heart J Suppl. 2019;21(Suppl K):K9-K20.
30. Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis. 2014;73(7):1340-9.
31. Souza R, Humbert M, Sztrymf B, Jais X, Yaici A, Le Pavec J, et al. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. Eur Respir J. 2008;31(2):343-8.
32. Savale L, Chaumais MC, Cottin V, Bergot E, Frachon I, Prevot G, et al. Pulmonary hypertension associated with benfluorex exposure. Eur Respir J. 2012;40(5):1164-72.
33. Simonneau G, Humbert M. Amphetamine Derivatives and the Risk of Pulmonary Arterial Hypertension. A New Chapter of the Story. American journal of respiratory and critical care medicine. 2018;197(6):704-6.
34. Stenmark KR, McMurtry IF. Vascular remodeling versus vasoconstriction in chronic hypoxic pulmonary hypertension: a time for reappraisal? Circ Res. 2005;97(2):95-8.
35. Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation. 1958;18(4 Part 1):533-47.
36. Jonigk D, Golpon H, Bockmeyer CL, Maegel L, Hoeper MM, Gottlieb J, et al. Plexiform lesions in pulmonary arterial hypertension composition, architecture, and microenvironment. Am J Pathol. 2011;179(1):167-79.
37. Wagenvoort CA. The pathology of primary pulmonary hypertension. J Pathol. 1970;101(4):Pi.
38. Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. European respiratory review : an official journal of the European Respiratory Society. 2010;19(115):59-63.

39. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The Relationship Between the Right Ventricle and its Load in Pulmonary Hypertension. J Am Coll Cardiol. 2017;69(2):236-43.
40. Girerd B, Weatherald J, Montani D, Humbert M. Heritable pulmonary hypertension: from bench to bedside. European respiratory review : an official journal of the European Respiratory Society. 2017;26(145).
41. Humbert M, Deng Z, Simonneau G, Barst RJ, Sitbon O, Wolf M, et al. BMPR2 germline mutations in pulmonary hypertension associated with fenfluramine derivatives. Eur Respir J. 2002;20(3):518-23.
42. Larkin EK, Newman JH, Austin ED, Hemnes AR, Wheeler L, Robbins IM, et al. Longitudinal analysis casts doubt on the presence of genetic anticipation in heritable pulmonary arterial hypertension. American journal of respiratory and critical care medicine. 2012;186(9):892-6.
43. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal. 2015;46(4):903.
44. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010;122(2):164-72.
45. McDonough A, Matura LA, Carroll DL. Symptom experience of pulmonary arterial hypertension patients. Clin Nurs Res. 2011;20(2):120-34.
46. Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):40S-7S.
47. Mercurio V, Peloquin G, Bourji KI, Diab N, Sato T, Enobun B, et al. Pulmonary arterial hypertension and atrial arrhythmias: incidence, risk factors, and clinical impact. Pulm Circ. 2018;8(2):2045894018769874.
48. Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic Consequences of Pulmonary Hypertension and Right-Sided Heart Failure. Circulation. 2020;141(8):678-93.
49. Chu JW, Kao PN, Faul JL, Doyle RL. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. Chest. 2002;122(5):1668-73.
50. Olsson KM, Nickel NP, Tongers J, Hoeper MM. Atrial flutter and fibrillation in patients with pulmonary hypertension. Int J Cardiol. 2013;167(5):2300-5.
51. Wanamaker B, Cascino T, McLaughlin V, Oral H, Latchamsetty R, Siontis KC. Atrial Arrhythmias in Pulmonary Hypertension: Pathogenesis, Prognosis and Management. Arrhythmia & Electrophysiology Review. 2018;7(1):43-8.
52. Tongers J, Schwerdtfeger B, Klein G, Kempf T, Schaefer A, Knapp JM, et al. Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. Am Heart J. 2007;153(1):127-32.
53. Tonelli AR, Alnuaimat H, Mubarak K. Pulmonary vasodilator testing and use of calcium channel blockers in pulmonary arterial hypertension. Respiratory Medicine. 2010;104(4):481-96.
54. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. The American review of respiratory disease. 1985;131(4):493-8.
55. Austin C, Alassas K, Burger C, Safford R, Pagan R, Duello K, et al. Echocardiographic assessment of estimated right atrial pressure and size predicts mortality in pulmonary arterial hypertension. Chest. 2015;147(1):198-208.
56. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol. 2002;39(7):1214-9.

57. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation. 2006;114(14):1482-9.
58. Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. Cochrane Database Syst Rev. 2017;1(1):CD011285.
59. Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. American journal of respiratory and critical care medicine. 2015;192(11):1373-86.
60. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation. 1984;70(4):580-7.
61. Hoeper MM, Sosada M, Fabel H. Plasma coagulation profiles in patients with severe primary pulmonary hypertension. Eur Respir J. 1998;12(6):1446-9.
62. Johnson SR, Mehta S, Granton JT. Anticoagulation in pulmonary arterial hypertension: a qualitative systematic review. Eur Respir J. 2006;28(5):999-1004.
63. Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation. 2014;129(1):57-65.
64. Preston IR, Roberts KE, Miller DP, Sen GP, Selej M, Benton WW, et al. Effect of Warfarin Treatment on Survival of Patients With Pulmonary Arterial Hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). Circulation. 2015;132(25):2403-11.
65. Henkens IR, Hazenoot T, Boonstra A, Huisman MV, Vonk-Noordegraaf A. Major bleeding with vitamin K antagonist anticoagulants in pulmonary hypertension. Eur Respir J. 2013;41(4):872-8.
66. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2012;31(10):1073-86.
67. Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes D, Jr., Kucheryavaya AY, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth Adult Heart Transplantation Report-2018; Focus Theme: Multiorgan Transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2018;37(10):1155-68.
68. Khan IY, Singer LG, de Perrot M, Granton JT, Keshavjee S, Chau C, et al. Survival after lung transplantation in systemic sclerosis. A systematic review. Respir Med. 2013;107(12):2081-7.
69. Glanville AR, Estenne M. Indications, patient selection and timing of referral for lung transplantation. Eur Respir J. 2003;22(5):845-52.
70. NHS England. National policy for targeted therapies for the treatment of pulmonary hypertension in adults (May 2014)2014 Feburary 2020.
71. Packer M. Therapeutic application of calcium-channel antagonists for pulmonary hypertension. Am J Cardiol. 1985;55(3):196B-201B.
72. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105-11.
73. Mueller-Mottet S, Stricker H, Domenighetti G, Azzola A, Geiser T, Schwerzmann M, et al. Long-term data from the Swiss pulmonary hypertension registry. Respiration. 2015;89(2):127-40.
74. Malhotra R, Hess D, Lewis GD, Bloch KD, Waxman AB, Semigran MJ. Vasoreactivity to inhaled nitric oxide with oxygen predicts long-term survival in pulmonary arterial hypertension. Pulm Circ. 2011;1(2):250-8.

75. Ghofrani HA, Pepke-Zaba J, Barbera JA, Channick R, Keogh AM, Gomez-Sanchez MA, et al. Nitric oxide pathway and phosphodiesterase inhibitors in pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):68S-72S.
76. Humbert M, Lau EM, Montani D, Jais X, Sitbon O, Simonneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. Circulation. 2014;130(24):2189-208.
77. Dupuis J, Hoeper MM. Endothelin receptor antagonists in pulmonary arterial hypertension. Eur Respir J. 2008;31(2):407-15.
78. Correale M, Ferraretti A, Monaco I, Grazioli D, Di Biase M, Brunetti ND. Endothelin-receptor antagonists in the management of pulmonary arterial hypertension: where do we stand? Vasc Health Risk Manag. 2018;14:253-64.
79. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. The New England journal of medicine. 1992;327(2):70-5.
80. LeVarge BL. Prostanoid therapies in the management of pulmonary arterial hypertension. Ther Clin Risk Manag. 2015;11:535-47.
81. Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. Eur Respir J. 2008;31(4):891-901.
82. Barnes H, Yeoh HL, Fothergill T, Burns A, Humbert M, Williams T. Prostacyclin for pulmonary arterial hypertension. Cochrane Database Syst Rev. 2019;5(5):CD012785.
83. Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. The New England journal of medicine. 2015;373(9):834-44.
84. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115(5):343-9.
85. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002;40(4):780-8.
86. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med. 1990;112(7):485-91.
87. (FDA) UFaDA. The voice of the patient. A series of reports from the U.S. Food and Drug Administration's (FDA's) patient-focused drug development initiative. Pulmonary arterial hypertension [Available from: http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM429382.pdf.
88. Humbert M, Sitbon O, Yaici A, Montani D, O'Callaghan DS, Jais X, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J. 2010;36(3):549-55.
89. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464-74.
90. Sandoval J, Bauerle O, Palomar A, Gomez A, Martinez-Guerra ML, Beltran M, et al. Survival in primary pulmonary hypertension. Validation of a prognostic equation. Circulation. 1994;89(4):1733-44.
91. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J. 2010;35(5):1079-87.
92. Graf S, Haimel M, Bleda M, Hadinnapola C, Southgate L, Li W, et al. Identification of rare sequence variation underlying heritable pulmonary arterial hypertension. Nat Commun. 2018;9(1):1416.
93. Evans JD, Girerd B, Montani D, Wang XJ, Galie N, Austin ED, et al. BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis. Lancet Respir Med. 2016;4(2):129-37.

94. Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. Eur Respir J. 2012;39(4):945-55.
95. Harari S. Out-of-proportion pulmonary hypertension: a paradigm for rare diseases. Chest. 2012;142(5):1087-8.
96. Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest. 1995;107(5):1193-8.
97. Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducolone A, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2005;172(2):189-94.
98. Thabut G, Dauriat G, Stern JB, Logeart D, Levy A, Marrash-Chahla R, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest. 2005;127(5):1531-6.
99. Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE, et al. Hemodynamic characterization of patients with severe emphysema. American journal of respiratory and critical care medicine. 2002;166(3):314-22.
100. Fossati L, Muller-Mottet S, Hasler E, Speich R, Bloch KE, Huber LC, et al. Long-term effect of vasodilator therapy in pulmonary hypertension due to COPD: a retrospective analysis. Lung. 2014;192(6):987-95.
101. Girard A, Jouneau S, Chabanne C, Khouatra C, Lannes M, Traclet J, et al. Severe pulmonary hypertension associated with COPD: hemodynamic improvement with specific therapy. Respiration. 2015;90(3):220-8.
102. Calcaianu G, Canuet M, Schuller A, Enache I, Chaouat A, Kessler R. Pulmonary Arterial Hypertension-Specific Drug Therapy in COPD Patients with Severe Pulmonary Hypertension and Mild-to-Moderate Airflow Limitation. Respiration. 2016;91(1):9-17.
103. Hurdman J, Condliffe R, Elliot CA, Swift A, Rajaram S, Davies C, et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. Eur Respir J. 2013;41(6):1292-301.
104. Valerio G, Bracciale P, Grazia D'Agostino A. Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2009;3(1):15-21.
105. Rao RS, Singh S, Sharma BB, Agarwal VV, Singh V. Sildenafil improves six-minute walk distance in chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial. The Indian journal of chest diseases & allied sciences. 2011;53(2):81-5.
106. Blanco I, Gimeno E, Munoz PA, Pizarro S, Gistau C, Rodriguez-Roisin R, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. American journal of respiratory and critical care medicine. 2010;181(3):270-8.
107. Goudie AR, Lipworth BJ, Hopkinson PJ, Wei L, Struthers AD. Tadalafil in patients with chronic obstructive pulmonary disease: a randomised, double-blind, parallel-group, placebo-controlled trial. Lancet Respir Med. 2014;2(4):293-300.
108. Vitulo P, Stanziola A, Confalonieri M, Libertucci D, Oggionni T, Rottoli P, et al. Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2017;36(2):166-74.
109. Farber HW, Miller DP, McGoon MD, Frost AE, Benton WW, Benza RL. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2015;34(3):362-8.
110. Holland AE, Spruit MA, Singh SJ. How to carry out a field walking test in chronic respiratory disease. Breathe (Sheff). 2015;11(2):128-39.
111. Morales FJ, Montemayor T, Martinez A. Shuttle versus six-minute walk test in the prediction of outcome in chronic heart failure. Int J Cardiol. 2000;76(2-3):101-5.

112. Lewis ME, Newall C, Townend JN, Hill SL, Bonser RS. Incremental shuttle walk test in the assessment of patients for heart transplantation. Heart (British Cardiac Society). 2001;86(2):183-7.
113. Ishrat R, Mujaddadi A, Ali MS, Talwar D, Hussain ME. Reliability and responsiveness of incremental shuttle walk test to estimate exercise capacity in patients with pulmonary arterial hypertension. Comparative Exercise Physiology. 2020:1-8.
114. Ertan Ö, Kuran Aslan G, Akinci B, Develi E, Okumus NG. The incremental shuttle walk test in pulmonary hypertension. European Respiratory Journal. 2019;54(suppl 63):PA1198.
115. Billings CG, Hurdman JA, Condliffe R, Elliot CA, Smith IA, Austin M, et al. Incremental shuttle walk test distance and autonomic dysfunction predict survival in pulmonary arterial hypertension. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2017;36(8):871-9.
116. Frost AE, Langleben D, Oudiz R, Hill N, Horn E, McLaughlin V, et al. The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. Vascul Pharmacol. 2005;43(1):36-9.
117. Sciurba FC, Slivka WA. Six-minute walk testing. Seminars in Respiratory and Critical Care Medicine. 1998;19(4):383-92.
118. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. American journal of respiratory and critical care medicine. 2002;166(1):111-7.
119. Force ERST, Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, et al. Recommendations on the use of exercise testing in clinical practice. Eur Respir J. 2007;29(1):185-209.
120. Weatherald J, Farina S, Bruno N, Laveneziana P. Cardiopulmonary Exercise Testing in Pulmonary Hypertension. Ann Am Thorac Soc. 2017;14(Supplement_1):S84-S92.
121. Vonk Noordegraaf A, Galie N. The role of the right ventricle in pulmonary arterial hypertension. European respiratory review : an official journal of the European Respiratory Society. 2011;20(122):243-53.
122. Watts JA, Marchick MR, Kline JA. Right ventricular heart failure from pulmonary embolism: key distinctions from chronic pulmonary hypertension. J Card Fail. 2010;16(3):250-9.
123. Naeije R, Manes A. The right ventricle in pulmonary arterial hypertension. European respiratory review : an official journal of the European Respiratory Society. 2014;23(134):476-87.
124. Potter LR. Natriuretic peptide metabolism, clearance and degradation. FEBS J. 2011;278(11):1808-17.
125. Buckley M, Marcus N, Yacoub M, Singer D. Prolonged stability of brain natriuretic peptide: importance for non-invasive assessment of cardiac function in clinical practice. Clin Sci (Lond). 1998;95:235-9.
126. Ordonez-Llanos J, Collinson PO, Christenson RH. Amino-terminal pro-B-type natriuretic peptide: analytic considerations. Am J Cardiol. 2008;101(3A):9-15.
127. Fu S, Ping P, Wang F, Luo L. Synthesis, secretion, function, metabolism and application of natriuretic peptides in heart failure. J Biol Eng. 2018;12:2.
128. Nagaya N, Nishikimi T, Okano Y, Uematsu M, Satoh T, Kyotani S, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol. 1998;31(1):202-8.
129. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation. 2000;102(8):865-70.
130. Leuchte HH, Holzapfel M, Baumgartner RA, Ding I, Neurohr C, Vogeser M, et al. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. J Am Coll Cardiol. 2004;43(5):764-70.
131. Fenster BE, Lasalvia L, Schroeder JD, Smyser J, Silveira LJ, Buckner JK, et al. Cystatin C: a potential biomarker for pulmonary arterial hypertension. Respirology. 2014;19(4):583-9.

132. Blyth KG, Groenning BA, Mark PB, Martin TN, Foster JE, Steedman T, et al. NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension. Eur Respir J. 2007;29(4):737-44.
133. Tulevski I, Groenink M, van der Wall EE, van Veldhuisen DJ, Boomsma F, Stoker J, et al. Increased brain and atrial natriuretic peptides in patients with chronic right ventricular pressure overload: correlation between plasma neurohormones and right ventricular dysfunction. Heart. 2001;86:27-30.
134. Gan CT, McCann GP, Marcus JT, van Wolferen SA, Twisk JW, Boonstra A, et al. NT-proBNP reflects right ventricular structure and function in pulmonary hypertension. Eur Respir J. 2006;28(6):1190-4.
135. Vonk Noordegraaf A, Westerhof N. Right ventricular ejection fraction and NT-proBNP are both indicators of wall stress in pulmonary hypertension. Eur Respir J. 2007;29(4):622-3.
136. Sitbon O, Benza RL, Badesch DB, Barst RJ, Elliott CG, Gressin V, et al. Validation of two predictive models for survival in pulmonary arterial hypertension. Eur Respir J. 2015;46(1):152-64.
137. McGoon MD, Benza RL, Escribano-Subias P, Jiang X, Miller DP, Peacock AJ, et al. Pulmonary arterial hypertension: epidemiology and registries. J Am Coll Cardiol. 2013;62(25 Suppl):D51-9.
138. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. Chest. 2019;156(2):323-37.
139. Anderson JJ, Lau EM, Lavender M, Benza R, Celermajer DS, Collins N, et al. Retrospective Validation of the REVEAL 2.0 Risk Score With the Australian and New Zealand Pulmonary Hypertension Registry Cohort. Chest. 2020;157(1):162-72.
140. Boucly A, Weatherald J, Savale L, Jais X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017;50(2):1700889.
141. Hoeper MM, Pittrow D, Opitz C, Gibbs JSR, Rosenkranz S, Grunig E, et al. Risk assessment in pulmonary arterial hypertension. Eur Respir J. 2018;51(3).
142. Kylhammar D, Kjellstrom B, Hjalmarsson C, Jansson K, Nisell M, Soderberg S, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J. 2018;39(47):4175-81.
143. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. The European Respiratory Journal. 2017;50(2):1700740.
144. Humbert M, Weatherald J. Right heart catheterisation is still a fundamental part of the follow-up assessment of pulmonary arterial hypertension. Eur Respir J. 2018;52(1):1800738.
145. Bustamante-Labarta M, Perrone S, De La Fuente RL, Stutzbach P, De La Hoz RP, Torino A, et al. Right atrial size and tricuspid regurgitation severity predict mortality or transplantation in primary pulmonary hypertension. J Am Soc Echocardiogr. 2002;15(10 Pt 2):1160-4.
146. Vonk-Noordegraaf A, Souza R. Cardiac magnetic resonance imaging: what can it add to our knowledge of the right ventricle in pulmonary arterial hypertension? Am J Cardiol. 2012;110(6 Suppl):25S-31S.
147. Geva T. Is MRI the preferred method for evaluating right ventricular size and function in patients with congenital heart disease?: MRI is the preferred method for evaluating right ventricular size and function in patients with congenital heart disease. Circulation Cardiovascular imaging. 2014;7(1):190-7.
148. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2000;2(4):271-8.
149. Anavekar NS, Gerson D, Skali H, Kwong RY, Yucel EK, Solomon SD. Two-dimensional assessment of right ventricular function: an echocardiographic-MRI correlative study. Echocardiography. 2007;24(5):452-6.

150. Peacock AJ, Crawley S, McLure L, Blyth KG, Vizza CD, Poscia R, et al. Changes in Right Ventricular Function Measured by Cardiac Magnetic Resonance Imaging in Patients Receiving Pulmonary Arterial Hypertension–Targeted Therapy. Circulation: Cardiovascular Imaging. 2014;7(1):107.
151. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol. 2011;58(24):2511-9.
152. van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J. 2007;28(10):1250-7.
153. Campo A, Mathai SC, Le Pavec J, Zaiman AL, Hummers LK, Boyce D, et al. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. American journal of respiratory and critical care medicine. 2010;182(2):252-60.
154. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation. 1992;86(2):513-21.
155. Tello K, Dalmer A, Axmann J, Vanderpool R, Ghofrani HA, Naeije R, et al. Reserve of Right Ventricular-Arterial Coupling in the Setting of Chronic Overload. Circ Heart Fail. 2019;12(1):e005512.
156. Vanderpool RR, Pinsky MR, Naeije R, Deible C, Kosaraju V, Bunner C, et al. RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. Heart (British Cardiac Society). 2015;101(1):37-43.
157. Swift AJ, Capener D, Johns C, Hamilton N, Rothman A, Elliot C, et al. Magnetic Resonance Imaging in the Prognostic Evaluation of Patients with Pulmonary Arterial Hypertension. American journal of respiratory and critical care medicine. 2017;196(2):228-39.
158. Bourantas CV, Loh HP, Bragadeesh T, Rigby AS, Lukaschuk EI, Garg S, et al. Relationship between right ventricular volumes measured by cardiac magnetic resonance imaging and prognosis in patients with chronic heart failure. Eur J Heart Fail. 2011;13(1):52-60.
159. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J. 2006;27(23):2879-88.
160. Swift AJ, Rajaram S, Campbell MJ, Hurdman J, Thomas S, Capener D, et al. Prognostic value of cardiovascular magnetic resonance imaging measurements corrected for age and sex in idiopathic pulmonary arterial hypertension. Circulation Cardiovascular imaging. 2014;7(1):100-6.
161. Munn Z, Moola S, Lisy K, Riitano D, Murphy F. Claustrophobia in magnetic resonance imaging: A systematic review and meta-analysis. Radiography. 2015;21(2):E59-E63.
162. Enders J, Zimmermann E, Rief M, Martus P, Klingebiel R, Asbach P, et al. Reduction of claustrophobia during magnetic resonance imaging: methods and design of the "CLAUSTRO" randomized controlled trial. BMC Med Imaging. 2011;11:4.
163. Do DH, Boyle NG. MRI in Patients with Implanted Devices: Current Controversies. http://www.acc.org/sitecore/content/Sites/ACC/Home/Latest-in-Cardiology/Articles/2016/08/01/07/15/MRI-in-Patients-with-Implanted-Devices [
164. Gardner BI, Bingham SE, Allen MR, Blatter DD, Anderson JL. Cardiac magnetic resonance versus transthoracic echocardiography for the assessment of cardiac volumes and regional function after myocardial infarction: an intrasubject comparison using simultaneous intrasubject recordings. Cardiovasc Ultrasound. 2009;7:38.
165. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J. 2004;147(2):218-23.
166. Bergemann R, Allsopp J, Jenner H, Daniels FA, Drage E, Samyshkin Y, et al. High levels of healthcare utilization prior to diagnosis in idiopathic pulmonary arterial hypertension support the feasibility of an early diagnosis algorithm: the SPHInX project. Pulm Circ. 2018;8(4):2045894018798613.

167. Sitbon O, Gomberg-Maitland M, Granton J, Lewis MI, Mathai SC, Rainisio M, et al. Clinical trial design and new therapies for pulmonary arterial hypertension. Eur Respir J. 2019;53(1):1801908.
168. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax. 1992;47(12):1019-24.
169. Kiely DG, Levin D, Hassoun P, Ivy DD, Jone PN, Bwika J, et al. EXPRESS: Statement on imaging and pulmonary hypertension from the Pulmonary Vascular Research Institute (PVRI). Pulm Circ. 2019;9(3):2045894019841990.
170. Hoey ET, Gopalan D, Ganesh V, Agrawal SK, Screaton NJ. Atrial septal defects: magnetic resonance and computed tomography appearances. J Med Imaging Radiat Oncol. 2009;53(3):261-70.
171. Bonnemains L, Mandry D, Marie PY, Micard E, Chen B, Vuissoz PA. Assessment of right ventricle volumes and function by cardiac MRI: quantification of the regional and global interobserver variability. Magn Reson Med. 2012;67(6):1740-6.
172. Saba TS, Foster J, Cockburn M, Cowan M, Peacock AJ. Ventricular mass index using magnetic resonance imaging accurately estimates pulmonary artery pressure. Eur Respir J. 2002;20(6):1519-24.
173. Ho ML, Bhalla S, Bierhals A, Gutierrez F. MDCT of partial anomalous pulmonary venous return (PAPVR) in adults. J Thorac Imaging. 2009;24(2):89-95.
174. Sears EH, Aliotta JM, Klinger JR. Partial anomalous pulmonary venous return presenting with adult-onset pulmonary hypertension. Pulm Circ. 2012;2(2):250-5.
175. Robicsek F, Daugherty HK, Cook JW, Selle JG. Sinus venosus type of atrial septal defect with partial anomalous pulmonary venous return. J Thorac Cardiovasc Surg. 1979;78(4):559-62.
176. Alsoufi B, Cai S, Van Arsdell GS, Williams WG, Caldarone CA, Coles JG. Outcomes after surgical treatment of children with partial anomalous pulmonary venous connection. Ann Thorac Surg. 2007;84(6):2020-6; discussion -6.
177. Hijii T, Fukushige J, Hara T. Diagnosis and management of partial anomalous pulmonary venous connection. A review of 28 pediatric cases. Cardiology. 1998;89(2):148-51.
178. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31(23):2915-57.
179. Jujo T, Tanabe N, Sugiura T, Naito A, Shigeta A, Kitazono-Saitoh M, et al. Importance of carefully interpreting computed tomography images to detect partial anomalous pulmonary venous return. Respir Investig. 2016;54(1):69-74.
180. Hoey ET, Lewis G, Yusuf S. Multidetector CT assessment of partial anomalous pulmonary venous return in association with sinus venosus type atrial septal defect. Quant Imaging Med Surg. 2014;4(5):433-4.
181. Haramati LB, Moche IE, Rivera VT, Patel PV, Heyneman L, McAdams HP, et al. Computed tomography of partial anomalous pulmonary venous connection in adults. J Comput Assist Tomogr. 2003;27(5):743-9.
182. Healey JE, Jr. An anatomic survey of anomalous pulmonary veins: their clinical significance. The Journal of thoracic surgery. 1952;23(5):433-44.
183. Majdalany DS, Phillips SD, Dearani JA, Connolly HM, Warnes CA. Isolated partial anomalous pulmonary venous connections in adults: twenty-year experience. Congenit Heart Dis. 2010;5(6):537-45.
184. Sahay S, Krasuski RA, Tonelli AR. Partial anomalous pulmonary venous connection and pulmonary arterial hypertension. Respirology. 2012;17(6):957-63.
185. Patel HR, Bhutani S, Shamoon F, Virk H. Deciphering a case of pulmonary hypertension in a young female: Partial anomalous pulmonary venous drainage the culprit. Ann Thorac Med. 2018;13(1):55-8.
186. El-Kersh K, Homsy E, Daniels CJ, Smith JS. Partial anomalous pulmonary venous return: A case series with management approach. Respir Med Case Rep. 2019;27:100833.

187. Pizzini A, Sonnwebber T, Frank R, Theurl M, Weiss G, Tancevski I, et al. Clinical Implications of Partial Anomalous Pulmonary Venous Connection: a rare cause of severe pulmonary arterial hypertensio. Pulm Circ. 2019;DOI: 10.1177/2045894019885352.
188. Condliffe R, Clift P, Dimopoulos K, Tulloh RMR. Management dilemmas in pulmonary arterial hypertension associated with congenital heart disease. Pulm Circ. 2018;8(3):2045894018792501.
189. Pearl RG, Siegel LC. Thermodilution cardiac output measurement with a large left-to-right shunt. J Clin Monit. 1991;7(2):146-53.
190. Weyland A, Wietasch G, Hoeft A, Buhre W, Allgeier B, Weyland W, et al. [The effect of an intracardiac left-right shunt on thermodilution measurements of cardiac output. An extracorporeal circulation model]. Der Anaesthesist. 1995;44(1):13-23.
191. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1).
192. Galie N, Channick RN, Frantz RP, Grunig E, Jing ZC, Moiseeva O, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J. 2019;53(1):1801889.
193. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 2012;142(2):448-56.
194. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53(1):1801914.
195. Montani D, O'Callaghan DS, Savale L, Jais X, Yaici A, Maitre S, et al. Pulmonary veno-occlusive disease: recent progress and current challenges. Respir Med. 2010;104 Suppl 1:S23-32.
196. Yorke J, Corris P, Gaine S, Gibbs JS, Kiely DG, Harries C, et al. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. Eur Respir J. 2014;43(4):1106-13.
197. Brewis MJ, Church AC, Johnson MK, Peacock AJ. Severe pulmonary hypertension in lung disease: phenotypes and response to treatment. Eur Respir J. 2015;46(5):1378-89.
198. Trip P, Nossent EJ, de Man FS, van den Berk IA, Boonstra A, Groepenhoff H, et al. Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. Eur Respir J. 2013;42(6):1575-85.
199. Olsson KM, Fuge J, Meyer K, Welte T, Hoeper MM. More on idiopathic pulmonary arterial hypertension with a low diffusing capacity. Eur Respir J. 2017;50(2):1700354.
200. Kirby M, Owrangi A, Svenningsen S, Wheatley A, Coxson HO, Paterson NA, et al. On the role of abnormal DL(CO) in ex-smokers without airflow limitation: symptoms, exercise capacity and hyperpolarised helium-3 MRI. Thorax. 2013;68(8):752-9.
201. Seimetz M, Parajuli N, Pichl A, Veit F, Kwapiszewska G, Weisel FC, et al. Inducible NOS inhibition reverses tobacco-smoke-induced emphysema and pulmonary hypertension in mice. Cell. 2011;147(2):293-305.
202. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JSR, et al. Changing Demographics, Epidemiology, and Survival of Incident Pulmonary Arterial Hypertension. American Journal of Respiratory and Critical Care Medicine. 2012;186(8):790-6.
203. Lau EM, Humbert M, Celermajer DS. Early detection of pulmonary arterial hypertension. Nat Rev Cardiol. 2015;12(3):143-55.
204. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. The New England journal of medicine. 2013;369(9):809-18.
205. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. The New England journal of medicine. 2015;373(26):2522-33.
206. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017;50(2):1700740.

207. Weatherald J, Boucly A, Sahay S, Humbert M, Sitbon O. The Low-Risk Profile in Pulmonary Arterial Hypertension. Time for a Paradigm Shift to Goal-oriented Clinical Trial Endpoints? American journal of respiratory and critical care medicine. 2018;197(7):860-8.
208. Hassoun PM, Zamanian RT, Damico R, Lechtzin N, Khair R, Kolb TM, et al. Ambrisentan and Tadalafil Up-front Combination Therapy in Scleroderma-associated Pulmonary Arterial Hypertension. American journal of respiratory and critical care medicine. 2015;192(9):1102-10.
209. Benza R, Biederman R, Murali S, Gupta H. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. J Am Coll Cardiol. 2008;52(21):1683-92.
210. van der Zwaan HB, Geleijnse ML, McGhie JS, Boersma E, Helbing WA, Meijboom FJ, et al. Right ventricular quantification in clinical practice: two-dimensional vs. three-dimensional echocardiography compared with cardiac magnetic resonance imaging. European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology. 2011;12(9):656-64.
211. Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. American journal of respiratory and critical care medicine. 2003;167(5):735-40.
212. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. American journal of respiratory and critical care medicine. 2009;179(7):615-21.
213. Yamada Y, Okuda S, Kataoka M, Tanimoto A, Tamura Y, Abe T, et al. Prognostic value of cardiac magnetic resonance imaging for idiopathic pulmonary arterial hypertension before initiating intravenous prostacyclin therapy. Circulation journal : official journal of the Japanese Circulation Society. 2012;76(7):1737-43.
214. Johns CS, Kiely DG, Rajaram S, Hill C, Thomas S, Karunasaagarar K, et al. Diagnosis of Pulmonary Hypertension with Cardiac MRI: Derivation and Validation of Regression Models. Radiology. 2019;290(1):61-8.
215. Lewis R, Billings C, Hurdman J, Smith I, Austin M, Armstrong I, et al. The Incremental Shuttle Walking Test Can Be Used to Risk Stratify Patients with Pulmonary Hypertension as Per the European Respiratory/Cardiac Society Guidelines. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2019. p. A2507-A.
216. Swift AJ, Rajaram S, Condliffe R, Capener D, Hurdman J, Elliot C, et al. Pulmonary artery relative area change detects mild elevations in pulmonary vascular resistance and predicts adverse outcome in pulmonary hypertension. Investigative radiology. 2012;47(10):571-7.
217. Gan CT, Lankhaar JW, Westerhof N, Marcus JT, Becker A, Twisk JW, et al. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. Chest. 2007;132(6):1906-12.
218. Foppa M, Arora G, Gona P, Ashrafi A, Salton CJ, Yeon SB, et al. Right Ventricular Volumes and Systolic Function by Cardiac Magnetic Resonance and the Impact of Sex, Age, and Obesity in a Longitudinally Followed Cohort Free of Pulmonary and Cardiovascular Disease: The Framingham Heart Study. Circulation Cardiovascular imaging. 2016;9(3):e003810.
219. Kawut SM, Lima JA, Barr RG, Chahal H, Jain A, Tandri H, et al. Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study. Circulation. 2011;123(22):2542-51.
220. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104(4):429-35.
221. Demir R, Kucukoglu MS. Six-minute walk test in pulmonary arterial hypertension. Anatol J Cardiol. 2015;15(3):249-54.
222. Provencher S, Chemla D, Herve P, Sitbon O, Humbert M, Simonneau G. Heart rate responses during the 6-minute walk test in pulmonary arterial hypertension. Eur Respir J. 2006;27(1):114-20.

223. Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, Spreeuwenberg MD, Postmus PE, Bogaard HJ. Exercise testing to estimate survival in pulmonary hypertension. Medicine and science in sports and exercise. 2008;40(10):1725-32.
224. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation. 2010;122(2):156-63.
225. McLaughlin VV, Gaine SP, Howard LS, Leuchte HH, Mathier MA, Mehta S, et al. Treatment goals of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D73-81.
226. Vachiery JL, Yerly P, Huez S. How to detect disease progression in pulmonary arterial hypertension. European respiratory review : an official journal of the European Respiratory Society. 2012;21(123):40-7.
227. Gaine S, Simonneau G. The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension. European respiratory review : an official journal of the European Respiratory Society. 2013;22(130):487-94.
228. Billings CG, Lewis R, Hurdman JA, Condliffe R, Elliot CA, Thompson AAR, et al. The incremental shuttle walk test predicts mortality in non-group 1 pulmonary hypertension: results from the ASPIRE Registry. Pulm Circ. 2019;9(2):2045894019848649.
229. Rubin LJ. The 6-minute walk test in pulmonary arterial hypertension: how far is enough? American journal of respiratory and critical care medicine. 2012;186(5):396-7.
230. Naeije R. The 6-min walk distance in pulmonary arterial hypertension: "Je t'aime, moi non plus". Chest. 2010;137(6):1258-60.
231. Billings CG, Lewis R, Armstrong IJ, Hurdman JA, Smith IA, Austin M, et al. Incremental Shuttle Walking Test Distance Is Reduced in Patients With Pulmonary Hypertension in World Health Organisation Functional Class I. Front Med (Lausanne). 2018;5:172.
232. Lewis RA, Johns CS, Cogliano M, Capener D, Tubman E, Elliot CA, et al. Identification of Cardiac Magnetic Resonance Imaging Thresholds for Risk Stratification in Pulmonary Arterial Hypertension. American journal of respiratory and critical care medicine. 2020;201(4):458-68.
233. Parreira VF, Janaudis-Ferreira T, Evans RA, Mathur S, Goldstein RS, Brooks D. Measurement properties of the incremental shuttle walk test. a systematic review. Chest. 2014;145(6):1357-69.
234. Wensel R, Francis DP, Meyer FJ, Opitz CF, Bruch L, Halank M, et al. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol. 2013;167(4):1193-8.
235. Shah SJ, Thenappan T, Rich S, Sur J, Archer SL, Gomberg-Maitland M. Value of exercise treadmill testing in the risk stratification of patients with pulmonary hypertension. Circ Heart Fail. 2009;2(4):278-86.
236. Dumitrescu D, Sitbon O, Weatherald J, Howard LS. Exertional dyspnoea in pulmonary arterial hypertension. European respiratory review : an official journal of the European Respiratory Society. 2017;26(145):170039.
237. Condliffe R. Living with pulmonary hypertension: quality not just quantity. Eur Respir J. 2011;38(3):512-3.
238. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. Qual Life Res. 2006;15(1):103-15.
239. McCollister D, Shaffer S, Badesch DB, Filusch A, Hunsche E, Schuler R, et al. Development of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT(R)) questionnaire: a new patient-reported outcome instrument for PAH. Respir Res. 2016;17(1):72.
240. Foster E, Guillen A, Lara K, Oh P, Popielnicki A, Walker G, et al. Linguistic Validation of The Emphasis-10 Questionnaire: A Patient-Reported Outcome Instrument For Assessing Qol In Pulmonary Hypertension (Ph). Value in Health. 2015;18(7):A744.

241. Odevoglu P, Demir R, Okumuş G, Küçükoğlu S, Kuran Aslan G. Evaluation of the Validity and Reliability of the Turkish Translation of the Emphasis-10 Questionnaire In Patients with Pulmonary Hypertension. ERS 2018 International Congress; Paris2018.
242. Favoccia C, Kempny A, Yorke J, Armstrong I, Price LC, McCabe C, et al. EmPHasis-10 score for the assessment of quality of life in various types of pulmonary hypertension and its relation to outcome. Eur J Prev Cardiol. 2019;26(12):1338-40.
243. National Audit of Pulmonary Hypertension, 10th Annual Report 2019 [updated 24th October 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-pulmonary-hypertension-audit/2019.
244. de Vet HC, Terwee CB, Ostelo RW, Beckerman H, Knol DL, Bouter LM. Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. Health Qual Life Outcomes. 2006;4(1):54.
245. Mathai SC, Suber T, Khair RM, Kolb TM, Damico RL, Hassoun PM. Health-related Quality of Life and Survival in Pulmonary Arterial Hypertension. Ann Am Thorac Soc. 2016;13(1):31-9.
246. McCabe C, Bennett M, Doughty N, MacKenzie Ross R, Sharples L, Pepke-Zaba J. Patient-reported outcomes assessed by the CAMPHOR questionnaire predict clinical deterioration in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Chest. 2013;144(2):522-30.
247. Cenedese E, Speich R, Dorschner L, Ulrich S, Maggiorini M, Jenni R, et al. Measurement of quality of life in pulmonary hypertension and its significance. Eur Respir J. 2006;28(4):808-15.
248. Meads DM, McKenna SP, Doughty N, Das C, Gin-Sing W, Langley J, et al. The responsiveness and validity of the CAMPHOR Utility Index. Eur Respir J. 2008;32(6):1513-9.
249. Gomberg-Maitland M, Thenappan T, Rizvi K, Chandra S, Meads DM, McKenna SP. United States validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2008;27(1):124-30.
250. Delcroix M, Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. European respiratory review : an official journal of the European Respiratory Society. 2015;24(138):621-9.
251. Chin KM, Gomberg-Maitland M, Channick RN, Cuttica MJ, Fischer A, Frantz RP, et al. Psychometric Validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Questionnaire: Results of the SYMPHONY Trial. Chest. 2018;154(4):848-61.
252. Fernandes CJ, Martins BC, Jardim CV, Ciconelli RM, Morinaga LK, Breda AP, et al. Quality of life as a prognostic marker in pulmonary arterial hypertension. Health Qual Life Outcomes. 2014;12(1):130.
253. Reis A, Santos M, Vicente M, Furtado I, Cruz C, Melo A, et al. Health-Related Quality of Life in Pulmonary Hypertension and Its Clinical Correlates: A Cross-Sectional Study. Biomed Res Int. 2018;2018:3924517.
254. Bussone G, Mouthon L. Interstitial lung disease in systemic sclerosis. Autoimmun Rev. 2011;10(5):248-55.
255. Launay D, Sitbon O, Le Pavec J, Savale L, Tcherakian C, Yaici A, et al. Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. Rheumatology (Oxford, England). 2010;49(3):490-500.
256. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet (London, England). 2002;360(9337):895-900.
257. Le Pavec J, Girgis RE, Lechtzin N, Mathai SC, Launay D, Hummers LK, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. Arthritis Rheum. 2011;63(8):2456-64.

258. Rajaram S, Swift AJ, Condliffe R, Johns C, Elliot CA, Hill C, et al. CT features of pulmonary arterial hypertension and its major subtypes: a systematic CT evaluation of 292 patients from the ASPIRE Registry. Thorax. 2015;70(4):382-7.

Appendix A: emPHasis-10 questionnaire

emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

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