LONG TERM OUTCOME, AETIOLOGICAL FACTORS AND PREDICTORS OF MORTALITY IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

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Thesis submitted to the University of Sheffield for the degree of Doctor of Medicine June 2021

To my family

This thesis has been composed by Syed Rehan Quadery and represents the culmination of three years' work at the Sheffield Pulmonary Vascular Disease Unit, Sheffield, UK. The work on which this thesis is based is the candidate's own, with assistance from other members of the department during the conduction of some of the studies. This thesis has not been submitted in candidature for any other degree, diploma or qualification.

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Date: 30.06.2021

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The University Of Sheffield.

Acknowledgements

I would like to thank all those who have helped me over the past three years at the Sheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital which has resulted in the submission of my thesis. I am grateful to Prof. David Kiely for providing me with the opportunity to work with him in this project. I appreciate his endless encouragement, support, guidance, patience, and the valuable time that he has invested in guiding me. This has helped me make a smooth transition from the clinical field into research. I would like to thank Cath Billings and Andy Swift who have provided teaching, training, and technical support on statistical analysis with SPSS. Dr. Robin Condliffe and Dr. Roger Thompson helped me critically appraise my work. In addition, Dr. Condliffe also provided helpful statistical advice. I would also like to thank Dr. Chris Johns for his technical support on statistical analysis with GraphPad software (Prism) and for his help with a figure showing the various imaging modalities in the diagnosis of CTEPH. Finally, I would like to thank Dr. Judith Hurdman and Sheila Forshaw for their invaluable help regarding the identification of patients and gathering of patient details. Judith also provided raw data for around 240 patients with CTEPH.

Abstract

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a serious debilitating condition that can be cured by pulmonary endarterectomy (PEA) surgery. Despite having effective treatment, a significant proportion of CTEPH patients do not undergo PEA surgery. There is limited information in the existing literature on the impact of these treatment decisions by the patients on their long-term survival.

This research retrospectively examines a large, contemporary cohort of consecutive, newly diagnosed, treatment-naïve patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were identified from the ASPIRE (Assessing the Spectrum of Pulmonary hypertension at a Referral centre) registry database. It compares the clinical course of different sub-groups of patients with CTEPH, with a focus on patients with technically operable disease who have not undergone surgery. I have described the baseline characteristics, investigations, and treatment received by the patients. I have also identified prognostic factors in different sub-groups of patients with CTEPH and compared their long-term survival following treatment.

In this study I have demonstrated that survival is better following PEA as compared to patients with technically operable disease not undergoing surgery as well as patients with a non-surgical disease distribution. I found that patients deemed unfit for surgery had a worse survival rate than patients who were offered surgery but declined, who in turn had a worse survival rate than patients presenting with other contributors to symptoms in addition to clot burden.

I also identified risk factors in patients that contributed to poor prognosis which might be useful in counselling patients and aid in clinical decision-making. Finally, I have shown that a non-invasive multimodal imaging approach can be helpful in PEA operability assessment in patients with CTEPH.

Plain Language Summary

Chronic thromboembolic pulmonary hypertension (CTEPH) occurs when blood clots in the lungs do not resolve. This causes the pressure in the lungs to rise. Without treatment CTEPH is a serious condition which significantly reduces life expectancy of the sufferer. CTEPH occurs in approximately 1 in 20 patients who have had a lung clot (also known as a pulmonary embolism). The condition is curable by a surgical procedure called pulmonary endarterectomy where the chronic lung clots are removed. However, not all patients are suitable for the operation and some patients who are suitable for the operation decline surgery. This study identifies several laboratory tests that can be used to identify patients at highest risk of poor prognosis and shows that surgery provides very good long-term results with respect to the survival rates of the patients. The findings of this study will help doctors better engage with patients suffering from CTEPH when discussing treatment options.

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Abbreviations

BPA	balloon pulmonary angioplasty
CI	cardiac index
CTEPH	chronic thromboembolic pulmonary hypertension
CTED	chronic thrombo-embolic disease
CTPA	computer tomography pulmonary angiogram
CCF	congestive cardiac failure
CPA	conventional pulmonary angiography
CAD	coronary artery disease
D_{LCO}	diffusion capacity of lung for carbon monoxide
DVT	deep vein thrombosis
ERA	endothelin receptor antagonists
HRCT	high resolution computer tomography
HRT	hormone replacement therapy
IPAH	idiopathic pulmonary arterial hypertension
ISWD	incremental shuttle walk distance
ISWT	incremental shuttle walk test
IBD	inflammatory bowel disease
IP-10	interferon-γ-induced protein-10
IL	interleukin
IQR	interquartile range
i/v	intravenous
LMWH	low molecular weight heparin
MRA	magnetic resonance pulmonary angiography
MMP	matrix metalloproteinase

Abbreviations (continued)

MIP	macrophage inflammatory protein
mPAP	mean pulmonary arterial pressure
mRAP	mean right arterial pressure
SvO_2	mixed venous oxygen saturations
MCP	monocyte chemotactic protein
MI	myocardial infarction
Nebs	nebulization
NOAC	novel oral anticoagulants
N	number of patients
OS	operating system
O	oral
OCP	oral contraceptive pill
PDE5i	phosphodiesterase 5 inhibitors
PGI_2	prostacyclin analogues
PAH	pulmonary arterial hypertension
PE	pulmonary embolism
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RAM	Random Access Memory
RCT	randomized controlled trial
RHC	right heart catheter
SPVDU	Sheffield Pulmonary Vascular Disease Unit
sGCs	soluble guanylate cyclase stimulator
SD	standard deviation

Abbreviations (continued)

S/C	subcutaneous
SPAP	systolic pulmonary arterial pressure
VTE	venous thromboembolism
V/Q	ventilation-perfusion
VA	ventriculo-atrial
VKA	vitamin K antagonist
WHO	World Health Organization

Publications and presentations to learned societies arising from the work in this thesis

Publications

1. **Quadery SR**, Swift AJ, Billings CG, Thompson AAR, Elliot CA, Hurdman J, Charalampopoulos A, Sabroe I, Armstrong IJ, Hamilton N, Sephton P, Garrad S, Pepke-Zaba J, Jenkins DP, Screaton N, Rothman AM, Lawrie A, Cleveland T, Thomas S, Rajaram S, Hill C, Davies C, Johns CS, Wild JM, Condliffe R, Kiely DG. The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension. Eur Respir J 2018 Sep; 52 (3): 1800589.

2. Condliffe R, **Quadery SR**, Jenkins DP, Armstrong IJ, Kiely DG. Decision-making in pulmonary endarterectomy surgery. Eur Respir J Jan 2019, 53 (1): 1801973.
3. **Quadery SR**, Swift AJ, Condliffe R, Billings C, Elliot CA, Charalampopoulos A, Sabroe I, Capener D, Pepke-Zana J, Jenkins DP, Screaton N, Rajaram S, Hill C, Johns CS, Wild, JM, Kiely DG. Successful outcome in chronic thromboembolic pulmonary hypertension using non-invasive imaging approach (under review).

Presentations to learned societies

1. **Quadery S**, Billings C, Wild J, Swift A, Rajaram S, Davies C, Hill C, Thomas S, Braidley P, Hunter S, Armstrong I, Hamilton N. Lawrie A, Hurdman J, Charalampopoulos A, Sabroe I, Condliffe R, Elliot C, Kiely DG. Chronic thromboembolic Pulmonary hypertension: Long term outcomes in operated and non-operated patients. European Respiratory Society meeting, London, September 2016. European Respiratory Journal Sep 2016 48 (suppl 60): PA 3605.
2. **Quadery S**, Condliffe R, Billings C, Thompson R, Elliot CA, Charalompopoulos A, Hurdman J, Hamilton N, Armstrong I, Sephton P, Sabroe I, Swift A, Wild J, Kiely DG. British Thoracic Society winter meeting, December 2016, London. P28 Chronic thromboembolic pulmonary hypertension: long term outcomes in surgical and non-surgical patients. Thorax 2016**;** 7: A98
3. **Quadery S**, Swift A, Billings C, Thompson A, Elliot C, Hurdman J, Garrod S, Charalampopoulos A, Sabroe I, Armstrong I, Hamilton N, Lewis R, Prasannan P, Jenkins D, Pepke-Zaba J, Screaton N, Lawrie A, Johns CS, Rajaram S Hill C, Wild JM, Condliffe R, Kiely DG. P183 Impact of patient choice on survival in patients with chronic thromboembolic pulmonary hypertension offered pulmonary endarterectomy. British Thoracic Society winter meeting, December 2017, London. Thorax 2017; 72**:** A181

Chapter 1. Chronic thromboembolic pulmonary hypertension: an overview

Introduction

Context

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, measured during right heart catheterization and is classified into five groups (table 1) (Galie et al., 2015). Group 1, also known as Pulmonary Arterial Hypertension (PAH) includes a cluster of conditions that share similar pathophysiology that can be treated with PAH specific targeted therapy (McGoon and Miller, 2012). Group 2 (Pulmonary Hypertension due to left heart disease), Group 3 (Pulmonary Hypertension due to lung diseases and or hypoxemia) and Group 5 (PH with unclear multifactorial mechanism) are more common than PAH, with treatment aimed at dealing with the underlying conditions (Galie et al., 2015).

The current study focuses on Group 4 PH. Also called chronic thromboembolic pulmonary hypertension (CTEPH), it is a severe but potentially curable form of pulmonary hypertension (Kim et al., 2013). It may follow an acute episode of pulmonary embolism (Lang et al., 2013, Pepke-Zaba et al., 2013a) but can also present as unexplained PH with no previous history of venous thromboembolism (Humbert M, 2010, Hoeper et al., 2006, Lang, 2004). Over the past 20 years the treatment of CTEPH has evolved significantly. Current protocols now include Pulmonary Endarterectomy (PEA) in operable cases (Jamieson SW, 2003) and PH specific therapy for inoperable disease (Simonneau et al., 2016, Jais et al., 2008, Suntharalingam et al., 2008, Reichenberger et al., 2007, Ghofrani et al., 2013, Simonneau, 2013, Simonneau, 2014). Balloon pulmonary angioplasty has also been considered as a potential alternative to surgery in selected patients (Mizoguchi et al., 2012, Feinstein et al., 2001, Inami et al., 2016, Galie et al., 2015).

Pulmonary endartarectomy (PEA) is the treatment of choice in CTEPH patients with operable disease with excellent symptomatic benefit and long term survival (Bonderman et al., 2007, Galie et al., 2015, Konstantinides, 2014). Analyses of large registries have shown a 10 year

survival of 72-75% in operated patients (Cannon et al., 2016, Madani et al., 2012). In contrast, treatment with anticoagulation alone in patients with mPAP of above 50 mmHg was found to result in a 5 year survival of only 10% (Lewczuk et al., 2001, Riedel M, 1982). PH specific targeted therapy with riociguat, a soluble guanylate cyclase stimulator (sGCs), has recently been licensed for the treatment of inoperable CTEPH disease in the UK. A recent Randomised controlled trial showed that patients with inoperable disease due or persistent PH post PEA had improved pulmonary haemodynamics and exercise capacity following pulmonary vasodilator therapy with riociguat with a 2 year survival of 93% (Ghofrani et al., 2013, Simonneau, 2013, Simonneau, 2014, Simonneau et al., 2016). The MERIT-1 trial examining the effects of macitentan versus placebo in patients with inoperable CTEPH have shown a decrease in PVR (at 16 week follow-up) and improvement in exercise capacity (at 24 week follow-up) (Ghofrani et al., 2017).

Despite excellent outcomes following surgery, a significant proportion of patients who have technically operable disease choose to not undergo surgery for a variety of reasons (Condliffe et al., 2008, Delcroix et al., 2016, Hurdman et al., 2012, Pepke-Zaba et al., 2011, Mayer et al., 2011, Escribano-Subias et al., 2016, Bunclark, 2017). To date only limited data exists on the clinical course of patients who have technically operable disease and do not undergo surgery.

In this thesis I have reviewed our current understanding of CTEPH and presented the predictors of mortality and long-term outcomes in a large cohort of patients with CTEPH. Furthermore, utilising the data on characteristics of patients with technically operable CTEPH who do not undergo surgery I have been able to identify prognostic factors that has the potential to inform patient choice and aid decision making.

Background

Definition of CTEPH

As per the most recent guidelines, for a diagnosis of CTEPH to be made, a patient needs to have an mPAP of ≥25 mm Hg and at least one (segmental) perfusion defect detected by perfusion lung scan or evidence of obstructions seen at CT angiography or conventional pulmonary angiography. Furthermore, patients should have received at least 3 months of effective anticoagulation. This is in order to discriminate this condition from 'sub-acute' Pulmonary embolism (PE). (Konstantinides, 2014, Kim, 2018b).

Classification of CTEPH

Thistlethwaite and co-workers have classified CTEPH into four types based on the intra-operative location of the thrombotic material. *Type 1* (fresh thrombus in main-lobar pulmonary arteries); *type 2* (intimal thickening and fibrosis proximal to the segmental arteries); *type 3* (disease within distal segmental arteries only); and *type 4* (distal arteriolar vasculopathy without visible thromboembolic disease). Disease types can also be grouped into proximal (type 1 and 2) and distal disease (type 3 and 4). It has been seen that patients diagnosed with proximal type disease at PEA have a better prognosis as compared to patients with distal type disease (Thistlethwaite et al., 2002).

CTEPH can also be classified pre-operatively utilising imaging techniques. They are grouped into proximal and distal disease by the distribution of obstructions in the pulmonary vasculature. Proximal CTEPH involves main, lobar, and segmental pulmonary arteries and is also termed operable disease. Distal CTEPH involves sub segmental or smaller pulmonary arteries and is termed in-operable disease as it is usually surgically inaccessible (Cannon JE, 2013). The current system of classification of CTEPH is shown in table 2.

Pathophysiology of CTEPH

Pulmonary arterial obstruction followed by pulmonary vascular remodelling is considered to be the primary contributor in the development of CTEPH. However, the pathogenesis of CTEPH has been found to be multifactorial. Research done on the subject implicate factors such as infection, abnormal immune responses and fibrinolysis, genetics and inflammation in the development of this condition (Galie et al., 2015, Satoh et al., 2017, Toshner, 2016, Planquette et al., 2018, Wilkens et al., 2018). The current understanding of the mechanisms leading to the development of CTEPH are shown in figure 1.

There are 2 main hypotheses regarding the aetiology of CTEPH. As per the 'embolic hypothesis', CTEPH is thought to occur as a consequence of a failure in clot resolution following an acute pulmonary embolism. The resulting fibrosis within the clot causing pulmonary vascular remodelling and secondary small vessel disease. This eventually leads to the development of pulmonary hypertension and right ventricular dysfunction (Humbert M, 2010). Thus, the embolic hypothesis is also called the 'two compartment model' (Moser and Braunwald, 1973).

An alternative to the 'embolic hypothesis' is the 'thrombotic hypothesis'. This hypothesis states that an arteriopathy with accompanying endothelial cell dysfunction and in-situ thrombosis resulting in pulmonary vascular occlusions is the primary process by which CTEPH occurs. These arteriopathies in turn perpetuate pulmonary vascular remodelling leading to the development of PH (Humbert M, 2010). However, the causal aetiology of CTEPH might be heterogeneous, with the embolic hypothesis the major contributor in patients with more proximal and surgical disease, while the thrombotic hypothesis may be more important in patients with distal and non-surgical disease.

Studies have also suggested that inflammation might have an important role to play in the development of the disease (Hassoun et al., 2009). Quark et al. found high plasma levels of

inflammatory mediators including CRP, IL-10, MCP-1, MIP-1α and MMP-9 in patients with CTEPH confirming its role in the development of the condition (Quarck et al., 2015). Zabini et al. similarly reported raised levels of inflammatory cytokines such as serum IP-10 in patients with CTEPH and IPAH. They also found an association between high serum IP-10 levels and poor pulmonary haemodynamics and exercise capacity in patients suffering from CTEPH (Zabini et al., 2014). Soon et al. found that high serum levels of inflammatory cytokines like IL-6 and IL-8 in patients with CTEPH could predict the risk of developing persistent PH post PEA (Soon et al., 2010). Langer and co-workers found that high cytokine levels such as TNF alpha in patients with CTEPH significantly fell within 24 hours after PEA surgery, thus suggesting a potential role in the development of the disease (Langer et al., 2004). It has been reported that merely having PH post PEA surgery does not significantly affect long-term outcome (Condliffe et al., 2009). However, more recent studies have suggested that significant residual PH is associated with a worse outcome (Delcroix et al., 2016) (Cannon et al., 2016). Rose and co-workers found increased production of mediators of neutrophil function in patients with CTEPH and IPAH. These were reduced by nebulised iloprost and was reflected clinically as an improvement in the pulmonary haemodynamics in both patient groups (Rose et al., 2003).

Although the role on inflammation in the development of CTEPH has been established by current research whether targeting inflammation is important in the treatment of established CTEPH or acute pulmonary embolism is currently unknown. Given that PEA can potentially cure CTEPH in selected patients, it can be surmised that for patients with established proximal surgical disease targeting inflammation might be of limited value.

Incidence & Prevalence of CTEPH

The exact incidence and prevalence of CTEPH is still largely unknown, although over the recent years there has been an increasing number of epidemiological studies exploring the subject. The UK audit provides a unique country-wide source of information on the relative prevalence of

CTEPH in different parts of the UK (GIBBS S et al., 2011). Analysis of an international registry by Pepke-Zaba et al. in 2013 reported an incidence of 5 per million of population per year in the UK (Pepke-Zaba et al., 2013b). However, approaches that target particular populations may increase diagnostic rates. De-Fonseka and co-workers showed that the annual incidence of CTEPH was 15 cases/million/year in the Sheffield city population. The Sheffield data included patients diagnosed through a dedicated PE clinic and those presenting with unexplained PH (De-Fonseka D, 2014). A recent report from Bath (UK) which was generated by developing a regional specialist PH service showed an incidence of CTEPH of 8.3 per million of population per year in that region (Suntharalingam, 2018).

Associated risk factors and prognostic indicators in CTEPH

CTEPH has been found to be associated with a variety of medical conditions, with some factors have prognostic significance. Incomplete resolution of clots has frequently been observed after an acute pulmonary embolus. The degree of obstruction to the pulmonary vasculature is low in most of the cases (Miniati et al., 2006, Planquette et al., 2018). A recent report from Switzerland suggested that the cumulative incidence of CTEPH two years after an acute PE could be as low as 0.79% (Coquoz et al., 2018). However, Pengo et al. found that the cumulative risk of developing CTEPH was 3.8% within 2 years after an acute PE (Pengo et al., 2004). Pepke-Zaba and co-workers showed that a history of VTE was the greatest risk factor in the development of CTEPH and was present in approximately 75% of patients. They found that thrombophilic disorders and family history of VTE were more common in patients who were considered operable. On the other hand, splenectomy, major surgery, CCF, and a history of cancer were more common in the non-operable group (Pepke-Zaba et al., 2011). Lang and co-workers found that risk factors for CTEPH included a history of acute VTE, large clot burden on imaging, non-O blood groups, and older age. In addition, they found that operability in patients with CTEPH was associated with younger age, proximal clots, and lower pulmonary vascular resistance (Lang et al., 2013). Condliffe et al. also found that a history of VTE was more

common in operable patients and previous history of splenectomy was more common in non-operable patients. Interestingly, they reported that associated medical conditions such as previous pacemaker lead, atrio-ventricular shunt, splenectomy and inflammatory bowel disease did not affect survival (Condliffe et al., 2009).

The pulmonary vascular resistance before PEA has also been found to be directly proportional to the perioperative mortality (Dartevelle et al., 2004). Jamieson and co-workers found that preoperative PVR was the largest risk factor for surgery and postoperative PVR was an important indicator of mortality in patients with CTEPH (Jamieson SW, 2003). A 2018 report from France showed that pre-operative PVR was a significant independent predictor of postoperative as well as three-year mortality (Tromeur et al., 2018). The international CTEPH registry showed that functional class IV, increased RAP, history of cancer and dialysis-dependent renal failure was associated with higher mortality in operated and non-operated patients. For operated patients, bridging therapy, persistent PH post-PEA, surgical complications post-PEA and additional cardiac procedures was associated with higher mortality rates. On the other hand, co-morbidities such as coronary artery disease, COPD and left heart failure were also associated with higher mortality in non-operated patients. However, a history of VTE and higher preoperative mPAP was found to be associated with a lower perioperative mortality. (Delcroix et al., 2016). Recent registry data from Europe suggested that the independent predictors of survival in patients with CTEPH (who did not undergo PEA surgery) and patients with persistent PH post PEA surgery who were treated with PH specific targeted therapy were WHO functional class and BNP/NT-pro BNP (Delcroix et al., 2018). Figure 2 is a diagrammatic representation of some of the known risk factors for CTEPH.

Clinical presentation of CTEPH

The clinical features of CTEPH are non-specific and are similar to the other forms of PH. Patients may be asymptomatic, particularly if their exercise capacity is limited by other

comorbidities. In the international CTEPH registry the commonest symptoms included dyspnoea (99%), oedema (41%), fatigue (32%), chest pain (15%) and syncope (14%) (Pepke-Zaba et al., 2011). It has been seen that the initial symptoms of the disease are often exertion induced and include breathlessness, tiredness, chest pain and syncope, with features of right ventricular dysfunction presenting in the advanced stages of the disease (Galie et al., 2015). It has been seen that patients with CTEPH present more frequently with oedema and haemoptysis whereas patients with IPAH present more frequently with syncope (Lang et al., 2013).

There may be a failure or relative delay in the diagnosis of this condition as a result of the non-specific symptoms particularly in patients with no history VTE which might contribute to poor long-term outcomes.

Investigations for CTEPH

There are a number of different investigations that can be performed in patients with suspected CTEPH and these depend on local expertise, availability of infrastructure and personal preference.

Ventilation-perfusion (V/Q) scan is recommended by international guidelines as the first-line investigation of choice for suspected CTEPH due to its of ease of interpretation and high sensitivity for surgical disease. It has a reported sensitivity and a specificity of 96-97% and 90-95% respectively for the diagnosis of CTEPH (Tunariu et al., 2007). There are, however, a number of limitations to V/Q imaging. Where there is web disease and good distal perfusion, V/Q scans might come out normal. It has been seen that the extent of perfusion defects also do not correspond well with the disease severity and the readily visible perfusion defects on V/Q scan can reduce over time in spite of worsening pulmonary haemodynamics (Moradi et al., 2019). An awareness of the benefits and limitations of various imaging modalities in the assessment of CTEPH is therefore important.

Computed tomographic pulmonary angiogram is another recognized imaging technique for the diagnosis of CTEPH (He J et al., 2012). High resolution computed tomography of the thorax helps visualize the lung parenchyma and may diagnose emphysema, bronchiectasis or pulmonary fibrosis. Mosaic attenuation is a common finding in patients with CTEPH but can also be seen in patients with IPAH (Sherrick et al., 1997). However, CTEPH might be missed when the tomogram is interpreted by individuals not experienced in pulmonary vascular diseases. A historical and often quoted manuscript by Tunariu et al. which used older CT techniques highlighted that a significant number of patients with CTEPH were missed on CTPA (Tunariu et al., 2007). More recent reports with modern techniques have shown excellent sensitivity of 95% and specificity of 95% when used in expert hands. This is comparable to V/Q scans (He J et al., 2012).

Magnetic resonance pulmonary angiogram exposes the patient to no radiation and is being increasingly used in the evaluation of suspected CTEPH as a replacement to CTPA. Rajaram and co-workers found a very high specificity and sensitivity profile of Contrast Enhanced MRA in diagnosing Chronic Thromboembolism (Rajaram et al., 2012). Another study by the same group found that sensitivity and specificity of 3D lung perfusion MRI in diagnosing CTEPH was very similar to Q-scan when images are interpreted by radiologists with experience with pulmonary vascular disease (Rajaram et al., 2013).

Right heart catheterisation is also an important diagnostic test that allows for the measurement of PVR. In order to identify potential surgical candidates, this measured elevation of PVR is compared to the degree of obstruction in the vascular bed which is observed by imaging techniques (Dartevelle et al., 2004). Patients with severe elevation of PVR and only modest obstruction of the pulmonary vasculature are at a high risk for surgical intervention (due to the presence of significant microvascular disease). A combination of drug therapy directed at the

pulmonary vasculature and balloon pulmonary angioplasty are the preferred techniques in this setting (Delcroix et al., 2021).

There is an increase in the number of patients with more distal disease profile who are undergoing pulmonary endarterectomy and Balloon Pulmonary Angioplasty (BPA) with good survival benefit. Hence, there is a greater focus on the assessment of the distal pulmonary vasculature. There are several different approaches to assessing the operability and suitability for balloon pulmonary angioplasty in CTEPH and the choice depends on the availability of the various modalities and the experience of different centres. Historically, studies have shown that V/Q scan and CTPA were the most accurate non-invasive investigations for the identification of CTEPH with a very high sensitivity and specificity (He J et al., 2012, Lang et al., 2010, Hoeper et al., 2005). More recent data has demonstrated the value of MR imaging and increasingly centres are using a multimodality imaging approach (Rajaram et al., 2013). Newer imaging modalities such as dual energy CT, cone beam CT, and area detector CT provide greater resolution of the distal pulmonary vasculature and may be more useful than invasive methods in planning surgeries (Kim, 2018b).

Conventional pulmonary angiography is recommended as the final diagnostic step in the workup of patients with CTEPH (Galie et al., 2015, Jenkins et al., 2012). Anterior–posterior and lateral views are generally utilised. Although conventional pulmonary angiography is considered the gold standard in determining the operability in CTEPH, it is being challenged by recent advances in non-invasive imaging techniques. CTPA is increasingly being used in the assessment of operability of CTEPH due to its high sensitivity (main/lobar pulmonary arteries: 89-100% and segmental pulmonary arteries: 84-100%) and specificity (main/lobar pulmonary arteries: 95-100% and segmental pulmonary arteries: 92-99%) in detecting thromboembolic lesions (Kim, 2018b). In some centres conventional pulmonary angiography is being replaced by MRA and CTPA which are non-invasive, cost effective procedures with fewer complications,

although, there is limited data on outcomes of patients selected for surgery using these approaches.

More recently the Fleischner society have reviewed the imaging approaches to diagnosing CTEPH and have highlighted the importance of a multi-modality approach to guide treatment decisions (Remy-Jardin et al., 2021). Whereas historically CTEPH has frequently been missed on CTPA, new CT imaging techniques allow for construction of perfusion maps (previously only visualised using scintigraphy). These perfusion maps can now be constructed using either dual energy CT or lung subtraction iodine maps on single energy scanners and improves the detection of CTEPH. Improvements in CT imaging techniques are now also being used to identify the proximal extent of thromboembolic disease. This data can be utilised to outline a road map for surgery. Conventional pulmonary angiography and digital subtraction angiography have previously been considered to be the reference standard for the assessment of CTEPH. However, recent advances in surgical techniques are allowing more distal disease to be tackled, thus enabling cone beam and ECG-gated CT to provide more precise information on the distal pulmonary vasculature and guide treatment.

Figure 3 shows an algorithm for the diagnostic approach for patients with CTEPH based on the 2015 European Society of Cardiology guidelines. Figure 4 demonstrates imaging features of CTEPH diagnosed using planar perfusion scintigraphy, dynamic contrast enhanced MR perfusion imaging, CTPA, and contrast enhanced MR angiography.

Management of CTEPH

General management of CTEPH

Standard medical treatment of CTEPH consists of long term anticoagulant therapy and diuretics with oxygen therapy in selected patients. Vitamin K antagonists like warfarin have historically been the preferred anticoagulant. However, an increasing number of patients are now treated with direct oral anticoagulants (DOAC). A report by Mutlu (Mutlu, 2017) involving 97 patients

(warfarin group, n=66 vs rivaroxaban group, n=31) suggested that rivaroxaban was as effective as warfarin in the prevention of venous thromboembolism in patient with CTEPH with no significant difference in bleeding rates. However, retrospective study by Bunclark et al. from the UK suggested a higher rate of recurrent VTE in patients treated with DOACs compared to warfarin (Bunclark et al., 2020). As of now, more information on DOACs from large scale prospective studies are required to measure its clinical effectiveness in patients with CTEPH. Including selective management, general preventive measures as for other forms of PH are important. These include vaccinations, encouragement of exercise, and counselling regarding the risks during pregnancy in women of child-bearing age. The treatment algorithm for chronic thromboembolic pulmonary hypertension based on the 2015 European society of cardiology guidelines is shown in figure 5.

PH specific targeted therapy

Trials have focused on patients with inoperable disease or persistent PH post-PEA. The BENEFiT randomised controlled trial showed significant improvement in pulmonary haemodynamics in these two patient groups when treated with bosentan after 16 weeks (Jais et al., 2008). However, this study did not show any improvement in exercise capacity in the bosentan group as compared to the placebo group. In an open labelled uncontrolled study Reichenberger et al. found patients with inoperable CTEPH taking sildenafil after 1 year of treatment showed significant improvement and maintenance in pulmonary haemodynamics and exercise capacity (Reichenberger et al., 2007). Riociguat is a soluble guanylate cyclase stimulator that has been licensed in Europe (including UK) for use in patients with inoperable CTEPH and persistent PH post PEA surgery. The CHEST 1 & 2 study showed significant improvement in exercise capacity and pulmonary haemodynamics in patients with inoperable disease or persistent PH post PEA taking riociguat as compared with placebo after 2 years of commencement of treatment. Patients receiving riociguat had an improvement in walk distance of 39 meters vs 6 meters in placebo group ($p<0.001$) and a reduction of PVR of 226

dyn·sec·cm–5 vs 23 dyn·sec·cm–5 in placebo group (p<0.001) at 16 weeks of follow-up. An extension of this study has shown maintenance of the improved exercise capacity for 2 years and a 2-year survival rate of 93% (Ghofrani et al., 2013, Simonneau et al., 2016). A multi-centre, randomised, double blind, placebo-controlled trial by Ghofrani and co-workers involving 80 patients with inoperable CTEPH (MERIT-1) demonstrated a decrease in PVR after 16 weeks of treatment with Mactentan, an endothelin receptor antagonist (ERA) as compared to placebo. They reported that PVR decreased to 73% of baseline in the macetentan group (n=34) vs 87% of baseline in the placebo group (n=40). The trial also showed improvement of 6-minute walk distance after 24 weeks of follow-up (35m in macitentan group vs 1 m in placebo group). Macitentan was well tolerated with only 23% of patients having peripheral oedema and 15% of patients having decreased haemoglobin (Ghofrani et al., 2017). Data from the OPUS (OPsumitUSers) registry by Kim and co-workers involving 40 patients with inoperable CTEPH on macitentan with median follow-up period of 15 months also showed a good safety profile. In this study only 5% patients had peripheral oedema and 2.5% patients developed anaemia (Kim, 2018b, Kim, 2018a).

PH specific targeted therapy are beneficial in patients with distal disease and persistent PH post PEA. However, to date very limited data exist on the clinical course of patients who have operable disease who do not undergo surgery and are on pulmonary vasodilator therapy. Table 3 shows the RCTs with PH specific targeted therapy in patients with distal disease and persistent PH post PEA.

Pulmonary endarterectomy (PEA)

Pulmonary endarterctomy (PEA) is the treatment of choice in patients with proximal CTEPH. It offers the most benefits with respect to improved quality and quantity of life (Bonderman et al., 2007) (Galie et al., 2015) (Konstantinides, 2014). The routine use of PEA in CTEPH is based on retrospective observational data from San Diego, USA where the 10 year survival following PEA

surgery was found to be 75% (Jamieson SW, 2003). This was a dramatic improvement as compared to historical cohorts where the 5 year survival was < 20% (Riedel M, 1982). Suitability for PEA surgery is generally determined by various factors which include the location of the occlusion and pulmonary haemodynamic measurements. Surgically accessible pulmonary vascular occlusions are proximal lesions and include the main, lobar and segmental arteries (Jenkins et al., 2017). The number of surgically accessible pulmonary vascular occlusions on multimodality imaging and imbalance between the pulmonary vascular resistance at right heart catheterization are important criteria in determining operability (Delcroix et al., 2021). In addition to these, advanced age, multiple co-morbidities, and poor general health condition are taken into consideration while assessing operability. There are no strict criteria for operability and patient selection and depends on the experience of the unit performing the procedure (Jenkins et al., 2017) although an expert PEA centre can perform more distal segmental pulmonary endarterectomies with less complications and excellent survival (Kim, 2018b) compared to less experienced centres (Kim, 2018b).

PEA is a potentially curative procedure (Kim et al., 2013). However, it is a major undertaking which requires a median sternotomy to be performed under total circulatory arrest with the patient on cardiopulmonary bypass under profound hypothermia (cooling to 20^{o} Celsius) (Jenkins et al., 2017). In terms of surgery, the usual approach is to perform an incision in the right main pulmonary artery and extend it to the right lower lobe. From there the organized thromboembolic material is dissected up to the subsegmental level (Jamieson SW, 2003). The residual layer after dissection of the organized clot is usually a pearly white smooth vessel wall (Jenkins et al., 2017). Circulatory arrest is restricted to 20-minute intervals while right-sided pulmonary endarterectomy is being performed and the procedure is usually completed within this time. Once the right sided endarterectomy is completed, the cardiopulmonary bypass is restarted, and patient is re-perfused while the incision of the right side is being closed. This procedure is repeated in the left side under similar conditions (Jamieson SW, 2003). The luminal

diameter of the PEA surgical specimens range between 5mm and 40mm (Southwood et al., 2016). The patients usually remain in hospital for 10-14 days following surgery (Taboada et al., 2014). The international prospective CTEPH registry suggested that the in-hospital mortality for patients undergoing PEA was relatively low, at around 4.7% (Pepke-Zaba et al., 2011). Cannon and co-workers reported an in-hospital mortality post PEA of 2-3% in a more recent cohort from the UK (Cannon et al., 2016). These provide increasing evidence that high volume PEA centres (performing > 50 cases per year) have significantly low postoperative mortality rates. Despite this, Pepke-Zaba et al. found that a significant proportion of patients with CTEPH were considered inoperable (Pepke-Zaba et al., 2011). Furthermore, a proportion of patients falling in the operable group did not undergo surgery.

Data from the various studies have shown excellent long-term survival in patients with operable disease following PEA very similar to those originally reported by Jamieson and colleagues in San Diego. Furthermore, the postoperative mortality has significantly reduced in the recent years. This may be attributed to the better selection of patients, refined surgical techniques, and advanced postoperative care.

Balloon pulmonary angioplasty

Balloon pulmonary angioplasty (BPA) is a treatment option in patients with inoperable CTEPH due to distal disease distribution or persistent PH post PEA surgery. BPA is a percutaneous interventional procedure performed by cardiologists who are specially trained in this procedure. It involves treating the pulmonary vascular occlusions with balloons at comparatively low pressures over a number of sessions. Each session is usually restricted to one lobe. This procedure is performed in selected centres in Europe where there is expertise but has been pioneered in Japan (Wilkens et al., 2018). This procedure has routinely been made available in the UK since April 2018. The Royal Papworth Hospital is the UKs first nationally designated centre for BPA (2018).

Feinstein and co-workers found improvements in pulmonary haemodynamics and clinical status in patients with inoperable CTEPH who had undergone BPA, albeit with higher complication rates of reperfusion pulmonary oedema and mechanical ventilation (Feinstein et al., 2001). Mizoguchi et al. reported similarly improved pulmonary haemodynamics and clinical status with lower complication and mortality rates in patients with inoperable CTEPH who underwent a refined technique of BPA (Mizoguchi et al., 2012). A report by Inami and co-workers involving 176 patients with CTEPH who underwent BPA (with a median follow-up period of 2.8 years) showed excellent long-term survival (five year survival of 95.5%) and maintenance of pulmonary haemodynamics (mPAP and PVR) over 3.5 years follow-up period (Inami et al., 2016). BPA has evolved as an acceptable and routinely practiced alternative in patients with CTEPH who are unable to undergo PEA surgery for various reasons including distal disease distribution and comorbidities, with excellent long-term survival, maintenance of pulmonary haemodynamics, reduced postoperative complications and improved exercise capacity. Increasingly BPA is also being considered as an adjunct to both medical and surgical therapy.

However, the role of BPA in patients with technically operable CTEPH who are unable to undergo PEA is still not clear (Kim, 2018b) (Galie et al., 2015). Research has recognised that there may be an overlay where patients may be suitable for either BPA or surgery. Increasingly, treatment approaches to CTEPH are including a multimodal approach where some patients may have surgery, BPA, and drug therapy (Delcroix et al., 2021).

Lung transplantation

Finally, lung transplantation may be an option in selected group of patients with CTEPH (absence of significant comorbidities and age below 60 years) who are deteriorating despite optimal treatment (Wilkens et al., 2018). There are a very limited number of donors for lung transplantation in the UK. Analysis of data from the UK national PH audit for 2018 found that

only three patients have undergone lung transplantation in that year (Gibbs, 2018). For this reason, the waiting list for lung transplantation in the UK is over a year.

Summary of Research focus

Aim of the study

The aim of the study was to describe the baseline characteristics, compare the long term survival and identify prognostic indicators in patients with CTEPH undergoing pulmonary endarterectomy (CTEPH-surgical-operated), technically operable disease not undergoing surgery (CTEPH-surgical-not-operated) and its sub-groups (declining surgery due to patient choice, lack of fitness for surgery and other contributors to symptoms in addition to clot burden) and technically in-operable disease (CTEPH-non-surgical-disease distribution). Patients with technically operable disease who have not undergone surgery and its sub-groups will be the primary focus of the study. Furthermore, this study aims to identify the rationale for treatment decisions in patients with technically operable disease who have not undergone surgery. It is anticipated that work from this thesis will help provide more up-to-date data on the long-term survival of patients with technically operable disease who have not undergone surgery and identify prognostic factors which may be helpful when counselling patients.

Conclusion

The field of CTEPH has evolved rapidly over the past two decades. However, despite much progress it still remains a debilitating condition for many. In addition, there remain unanswered questions regarding the long-term survival of patients with technically operable disease who have not undergone surgery. The work from this study will help provide more up-to-date prognostic data on the long-term survival of patients with technically operable disease who have not undergone surgery which will be helpful in discussions regarding the various treatment options.

Table 1: Classification of pulmonary hypertension (Galie et al., 2015)

Group	Nomenclature
1	Pulmonary arterial hypertension
2	Pulmonary hypertension due to left heart disease
3	Pulmonary Hypertension due to lung disease and /or hypoxia
4	Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
5	Pulmonary hypertension with unclear and/or multifactorial mechanisms

Table 2: Surgical classification of CTEPH ((Madani, 2016).

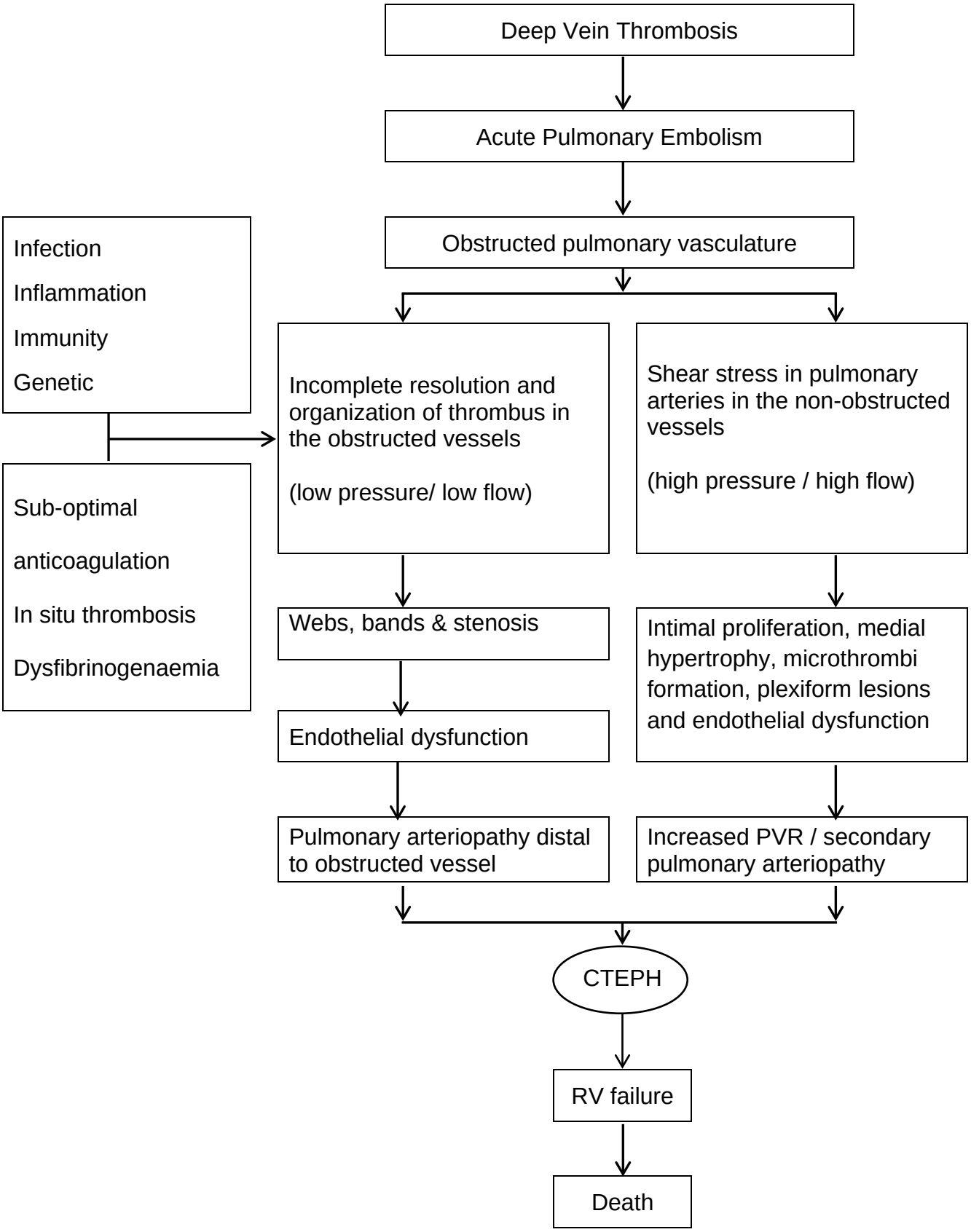
Disease type	Distribution of clot
0	No evidence of clot
I	At the level of the main pulmonary arteries
II	At the level of the lobar and intermediate pulmonary arteries
III	At the level of segmental arteries only
IV	At the level of subsegmental branches only

Table 3: Medical therapy in CTEPH (Kim, 2018b)

SN	RCT name	PH therapy	Class of Drug	Follow-up (weeks)	Total number of patients	Baseline functional class (NYHA FC)	Baseline Walk distance (6MWD in metres)	Change in Walk distance (6MWD in metres)	Baseline PVR (dyn-sec-cm-5)	Change in PVR (dyn-sec-cm-5)	Author– year of publication
1	BENEFIT	Bosentan	ERA	16	157	II-IV	342 (84)	+2 (NS)	778(323)	-24	(Jais et al., 2008)
2	CHEST-1	Riociguat	sGCs	16	261	II-IV	347 (80)	+46	787 (422)	-31	(Ghofrani et al., 2013),
3	MERIT-1	Macitentan	ERA	16/24	80	II-IV	352 (81)	+34	957 (435)	-16	(Ghofrani et al., 2017)

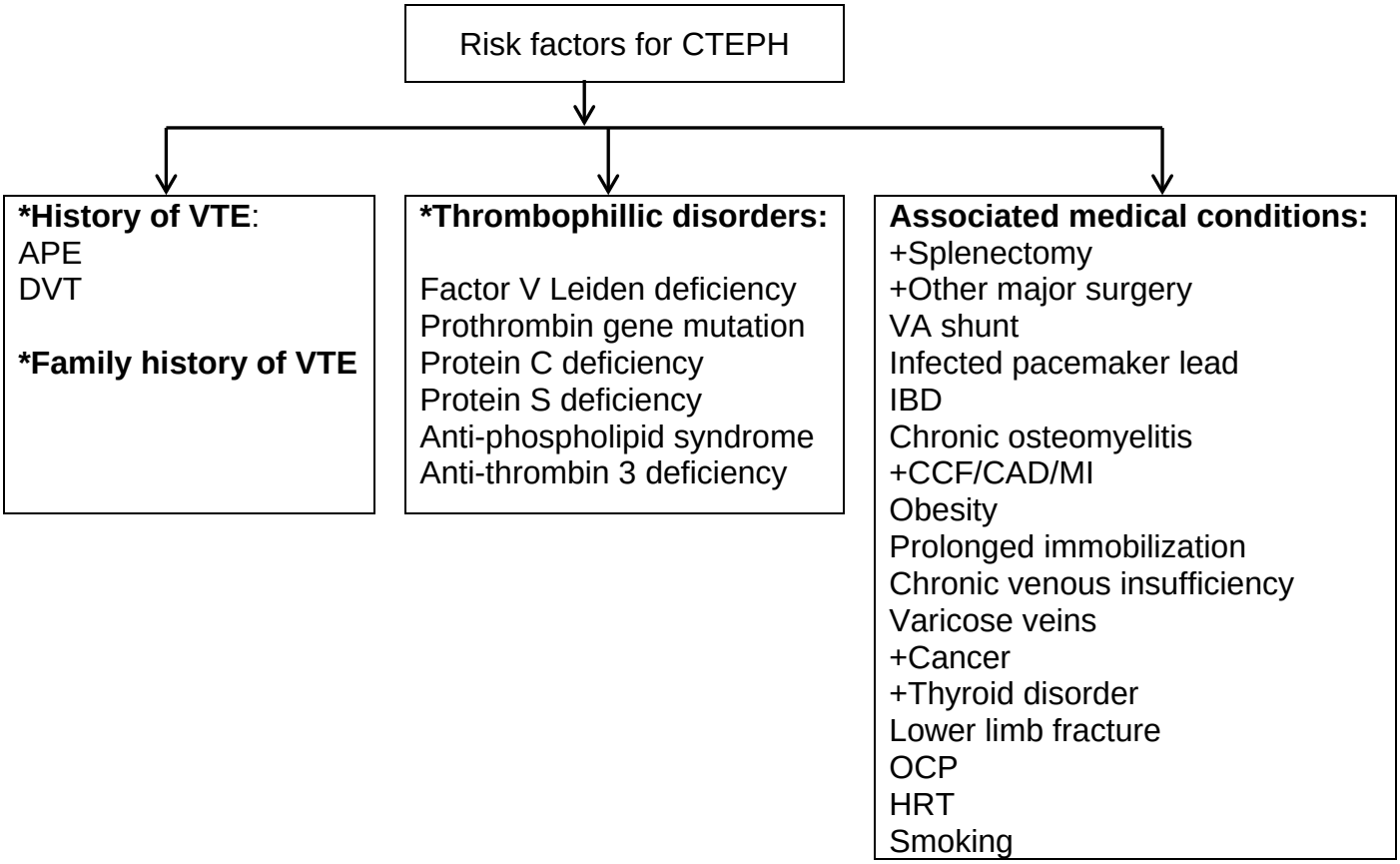
Definition of abbreviations; SN = serial number; RCT = randomised controlled trial; CTEPH = chronic thromboembolic pulmonary hypertension; ERA = endothelin receptor antagonist; sGCs = soluble guanylate cyclase stimulator; NYHA = New York Heart Association Functional Class; 6MWD = six-minute walk distance; NS = non-significant; PVR = pulmonary vascular resistance;

Figure 1: Pathophysiology of CTEPH (Lang et al., 2016)



Definition of abbreviations; CTEPH = chronic thromboembolic pulmonary hypertension; PVR = pulmonary vascular resistance; RV failure = right ventricular failure;

Figure 2: Risk factors for CTEPH

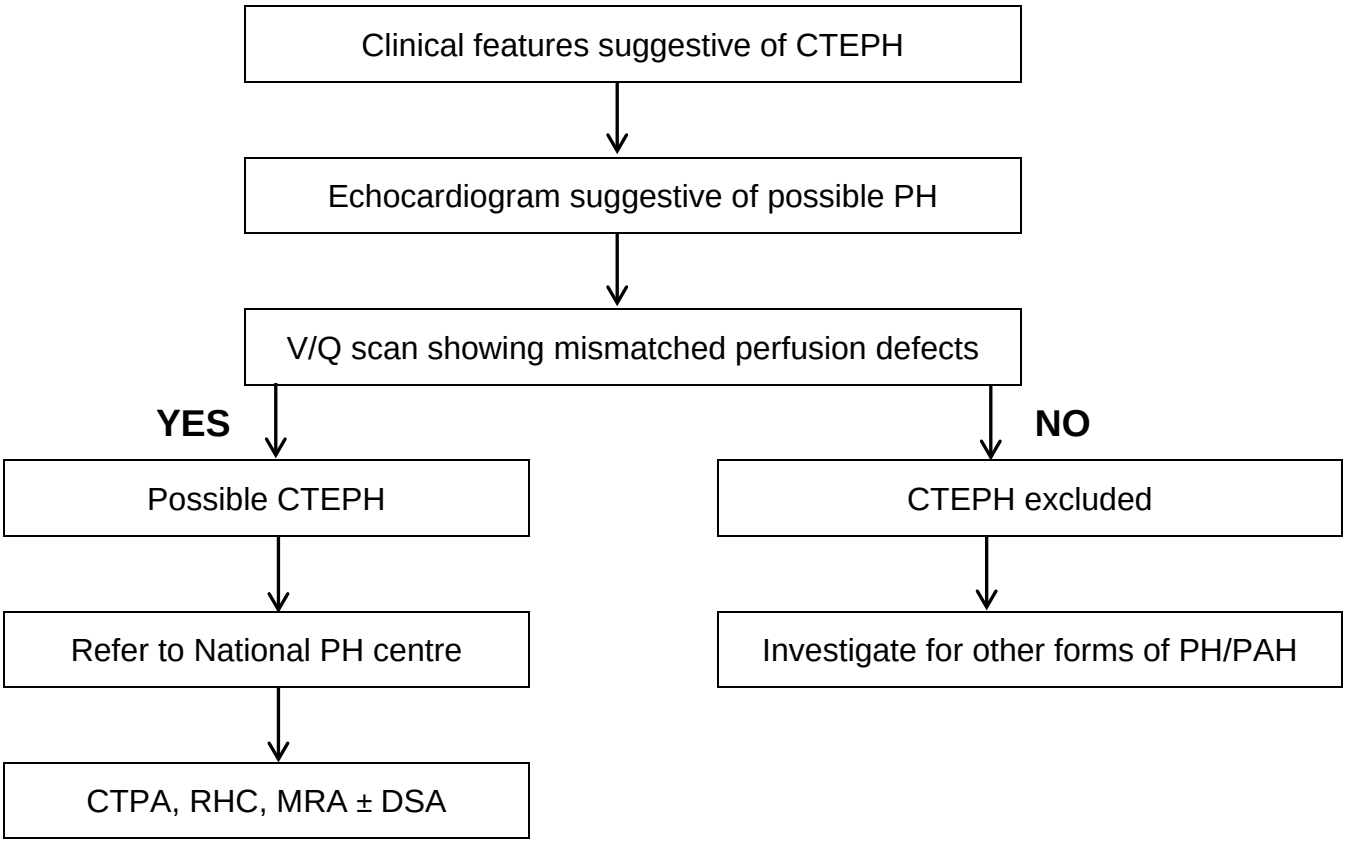


* More common in patients with operable disease

+ More common in patients with in-operable disease

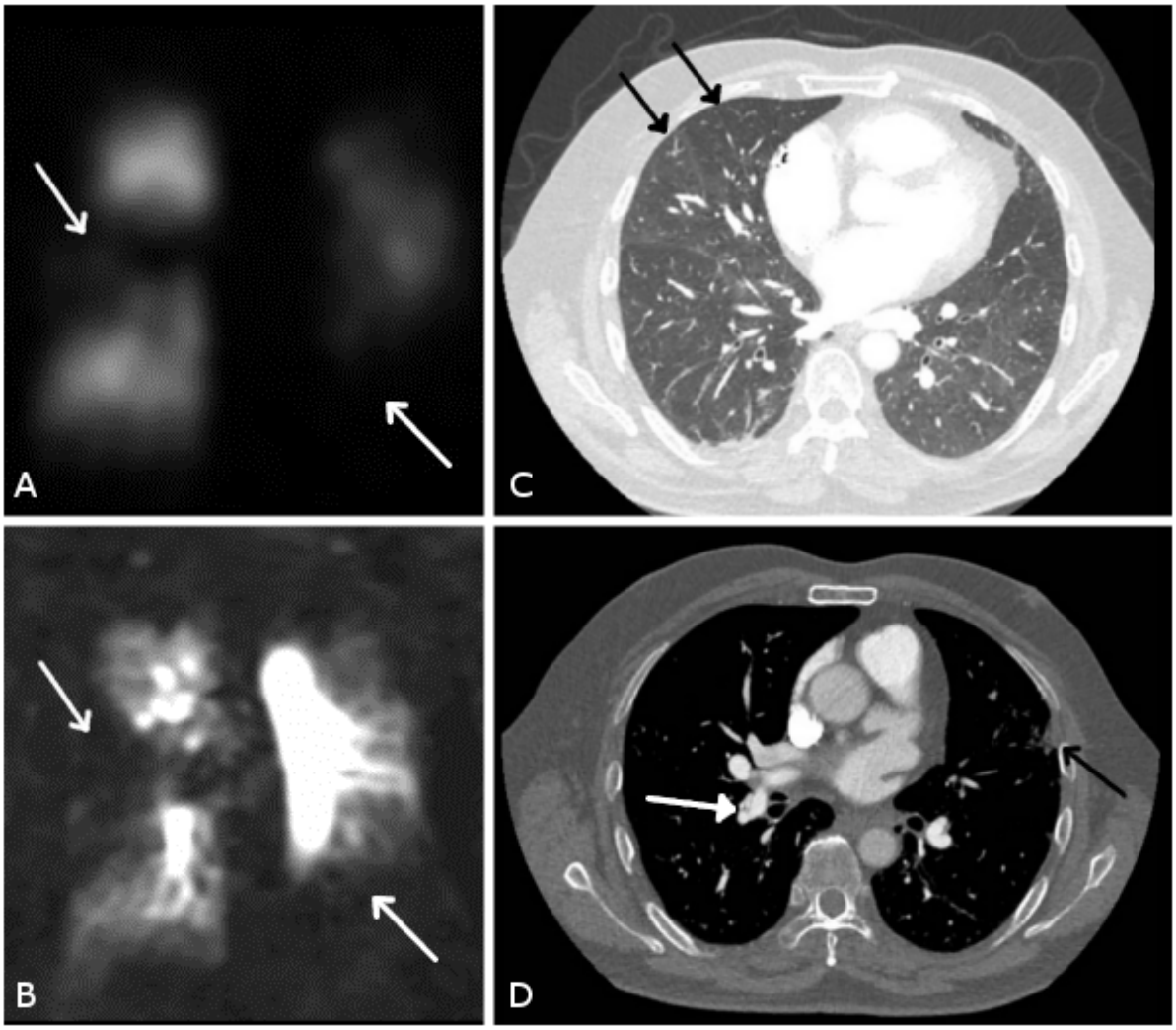
Definition of abbreviations; CTEPH = chronic thromboembolic pulmonary hypertension; VTE = venous thromboembolism; APE = acute pulmonary embolism; VA = ventriculo-atrial; CCF = congestive cardiac failure; CAD = coronary artery disease; MI = myocardial infarction; OCP = oral contraceptive pill; HRT = hormone replacement therapy;

Figure 3: Algorithm for diagnostic approach for patients with CTEPH(Galie et al., 2015)



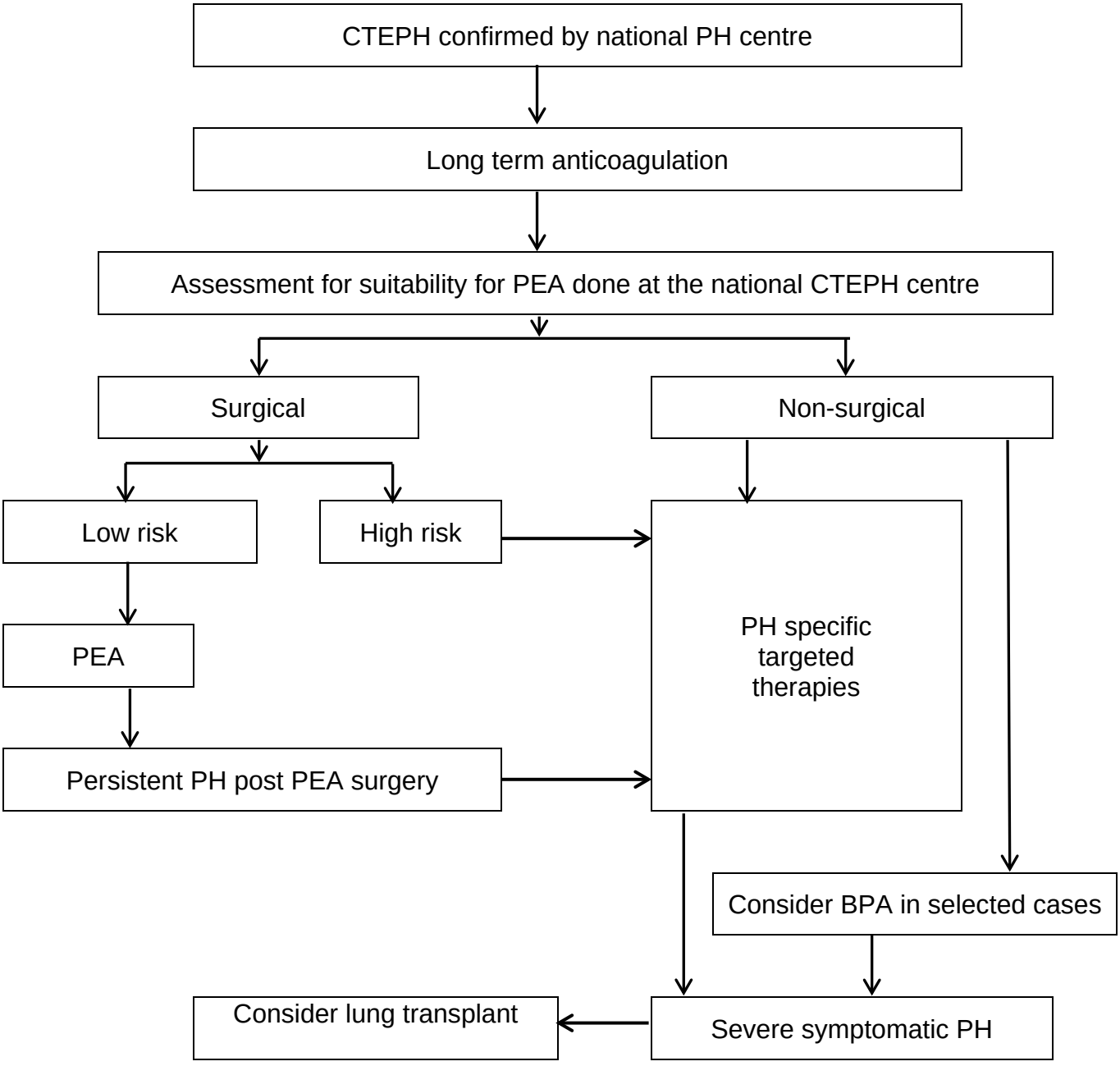
Definition of abbreviations; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension; V/Q = ventilation – perfusion; PAH = pulmonary arterial hypertension; CTPA = computed tomography pulmonary angiogram; RHC = right heart catherisation; MRA = magnetic resonance angiography; DSA = digital subtraction angiography;

Figure 4: Non-invasive multimodality imaging in chronic thromboembolic disease.



Non-invasive multimodality imaging in chronic thromboembolic disease. Bilateral segmental perfusion defects (white arrows) demonstrated on (A) planar perfusion scintigraphy, (B) 3D dynamic contrast enhanced perfusion MRI and (C and D) CTPA with the typical findings of a central filling defect (web) (white arrow), mosaic perfusion pattern (black arrow) and subpleural scarring from infarction (black arrows).

Figure 5: Treatment algorithm for chronic thromboembolic pulmonary hypertension (Galie et al., 2015)



Definition of abbreviations; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension; PEA = pulmonary endarterctomy; BPA = balloon pulmonary angioplasty;

Chapter 2. Methodology

Introduction

A patient registry can be defined as “an organized system that uses observational study methods to collect uniform data (clinical and other) and to evaluate specified outcomes for a population defined by a particular disease, condition or exposure and that serves one or more predetermined scientific, clinical, or policy purposes” (Gliklich and Campion, 2010). The purpose of a patient registry is to describe the clinical course of the disease, evaluate clinical or cost effectiveness in the day-to-day practice of medicine, assess risk, and determine the quality of care. The major advantage of a patient registry is that it is generally inexpensive. Also, being consecutive in nature it might reduce selection bias. Disadvantages of a patient registry include the quality of the information collected that may be variable or inaccurate, an inability to accurately compare outcomes between groups, and a difficulty in adjusting for confounding factors, despite the availability of modern statistical methods (Gliklich and Campion, 2010). Table 4 highlights important registries in patients with CTEPH.

Previous and current registries with a focus on CTEPH

Registries have shown poor long-term survival in CTEPH if left untreated or on anti-coagulation alone. These included patients with mild forms of the condition, patient with distal disease, and patients with technically operable disease not undergoing surgery (Riedel M, 1982, Lewczuk et al., 2001). The first PEA surgery was performed by Moser and Braunwald in UC San Diego in the 1971 and since then the San Diego group have performed over 3000 PEAs. From the UC San Diego registry data it can be identified that the prognosis of patients have improved remarkably with PEA with the most recent data suggesting a postoperative mortality of only around 1% (Jamieson SW, 2003, Madani et al., 2012). The UK national PEA programme based at the Royal Papworth Hospital have performed over 2000 PEAs since 1996 with a postoperative mortality of around 2.2%. Using their registry data, Cannon and co-workers looked primarily at the long-term survival and prognostic indicators in patients undergoing PEA

(Cannon et al., 2016). In a UK wide registry Condliffe et al. compared the long-term survival and prognostic indicators in patients with CTEPH who underwent PEA surgery with patients who were considered inoperable due to distal disease distribution and reported similar findings (Condliffe et al., 2008, Condliffe et al., 2009). Similar findings were also obtained by the analysis of the International CTEPH registry data by Delcroix & Pepke-Zaba and co-workers involving European countries as well as North America (Canada) (Pepke-Zaba et al., 2011, Delcroix et al., 2016). Delcroix et al. also assessed the survival and prognostic indicators in patients with CTEPH not undergoing PEA surgery or BPA as compared to patients with persistent PH post PEA surgery receiving PH-specific targeted therapy (Delcroix et al., 2018). Similar studies with similar results have also been reported by smaller registries in Europe (Escribano-Subias et al., 2016). Registry data of patients with inoperable CTEPH undergoing BPA have also shown excellent survival (Inami et al., 2016).

The UK National audit is hosted by NHS digital and commissioned by NHS England. Data is collected prospectively by all adult centers and the national children's center for PH at Great Ormond Street. There are over 30,000 patients with all forms of pulmonary hypertension including over 3000 patients with CTEPH enrolled in the national audit since 2009. This audit also confirms the excellent long-term survival following surgery with low surgical mortality rates (Kiely DG, 2021).

Interestingly, a thorough search of the existing literature did not find any research that specifically looked at the long-term survival and prognostic indicators in patients with technically operable CTEPH not undergoing surgery and its sub-groups (patient choice of declining surgery, being unfit for surgery and patients with mild disease). Furthermore, there are no comparisons of the long-term survival of patients with CTEPH who underwent surgery versus patients who had technically operable CTEPH who declined surgery.

Patient pathway in the management of CTEPH in the UK

In the UK there are eight nationally designated Pulmonary Hypertension (PH) centres across five cities. They include London (Great Ormond Street Hospital for children, Royal Free Hospital, Hammersmith Hospital and Royal Brompton Hospital), Glasgow (Golden Jubilee Hospital), Newcastle (Freeman Hospital), Cambridge (Royal Papworth Hospital), and Sheffield (Royal Hallamshire Hospital). Each centre acts as a referral centre for a specific geographical area in the UK and has a team of experts (physicians, radiologists, specialist nurses) qualified to investigate and treat patients with PAH and CTEPH (Gibbs, 2018). Importantly, each centre needs to adhere to national standards of care and results are published annually in the UK audit (Kiely DG, 2021)

The Sheffield Pulmonary Vascular Disease Unit (SPVDU) is the largest nationally designated PH centre in the UK, having over 2,000 active patients with PH (including PAH and CTEPH) (Gibbs, 2018). In Sheffield patients are referred from the Midlands, North West, Yorkshire and Humber, and Wales, covering a referral population of approximately fifteen to twenty million. The Royal Papworth Hospital, Cambridge is the UK's national PEA centre, receiving referrals of patients with CTEPH (for PEA and BPA) from all of UK's PH centres. It has performed over 2000 PEAs since 1996 (Papworth Hospital) with 166 PEAs performed between 2017 and 2018 reporting excellent long-term survival (Cannon et al., 2016, Gibbs, 2018) . The pathway for the management of CTEPH at the SPVDU is outlined in figure 6 and the follow-up management post-PEA at the national centre is outlined in table 5.

Establishing a database for collection of CTEPH data

Background

Data for the current study was initially intended to be collected into the ArQ PH research database. This is a data collection software created by the medical informatics and medical physics team at the Royal Hallamshire Hospital on behalf of the University of Sheffield, School

of Medicine and Sheffield Teaching Hospitals NHS Foundation Trust for research into patients with all forms of pulmonary hypertension (PH). I worked with my colleagues at the University of Sheffield and the local software developers to create new fields within the existing ArQ PH research database to meet the requirements for the proposed study. After having worked for 6 months with this project it was realized that within the available time frame it could not guaranteed that this database would be complete to allow for the completion of this study. The previous ASPIRE 1 registry was then considered to input the data. The ASPIRE registry 1 was a departmental database using Microsoft Access and was created to collect data for patients with all forms of PH. However, the ASPIRE 1 registry was found to not be suitable for the study as it did not have all the required fields and consequently I opted to develop a specific database for the purpose of this study.

Creation of a new database: ASPIRE 2 registry

After doing extensive research into the development of data collection software I opted to create a new database with the help of external software developers. The data collection software was required to be simple to use, secure, specific, valid, reliable, cost effective, with IT backup support and in accordance with the Trust's information governance policy. I chose Renvir to design the ASPIRE CTEPH registry database. Renvir is a subsidiary of Electronic Business Solution Limited. The software was initially created as a web-based interface which could store the data. Later due to potential concerns regarding the safety of data it was converted into a desktop application. The database was developed using Windows Form application (C#.NET) and Microsoft SQL Server 2008 (Express Edition). System requirements to run the applications included a minimum operating system (OS) of Windows 7 and a random-access memory (RAM) of 2 GB. I carried out pilot data collection and made further changes and alterations to the software during the developmental and troubleshooting stages of the project. Following an initial pilot of data entry from 10 patients I employed a significant update to the software with subsequent smaller modifications and refinements before it was ready to be used for this study.

The entire development process took 12 months.

The developmental process of the ASPIRE 2 registry database included a number of meetings with my academic supervisor to agree upon the variables to be captured in the new database based on previous literature and expert opinion. The detailed sequence of events has been summarised in the following steps.

a) Extensive search of the CTEPH literature and previous registries was done to identify key variables to be collected and identification of additional variables relevant to the specific area of study.
b) Use of an Excel format to display variables and time points was decided upon.
c) Several meetings were conducted with Trust and University IT department to ensure that clinical governance processes were followed with safety of data and data confidentiality, which were key components of the study. Subsequent discussion within the Trust to develop an in-house bespoke system to allow for ease of data collection and simple extraction of data to Excel to allow for analysis using standard statistical packages was done. Due to cost and time pressures it was established that the Trust would be unable to support development of this database.
d) Extensive research was performed to identify an external software developer in the UK and abroad. An external software developer in Bangladesh was identified that was able to deliver the planned configuration of the database. A contract with the software developers regarding creation of data collection software and provision of backup IT support and maintenance for one year was established at a cost of 1200 GBP. It was specified that the database should be user friendly and could be used for future prospective and retrospective data collection in patients with CTEPH.
e) Permissions were obtained from Sheffield University Hospitals NHS FT IT department to install software applications on Trust computers.

f) Multiple remote meetings with software developers were conducted regarding the development of the bespoke database.

g) With the help of TEAMVIEWER I was able to facilitate the software developers to remotely enter a Trust laptop and install the programme and provide the initial login ID and password (which was later changed).

h) Initial pilot data entry of 10 patients was done. The data was exported it to Excel format where I found multiple problems, including certain data which were entered into the database but did not appear in the spreadsheet after exporting.

i) Multiple further changes were identified to be made for the improvement of the database configuration and usability.

j) Further discussions were conducted with the software developer through TEAMVIEWER and telephone regarding the problems faced and corrections.

k) Discussions done with Trust IT department on whether certain data such as bloods tests, pulmonary function tests, right heart catheter studies and cardiac MRI results could be directly imported to the database. It was informed by IT department that this was not possible at that time. I discussed it with my academic supervisor who agreed to input these data manually.

l) Initially software was web based but due to potential data protection issues academic supervisor suggested making it computer based which was implemented.

m) Had a further pilot data of 40 patients entered into the database and reviewed the exporting of the data to Excel format. More issues were identified including disappearance of certain variables in the spreadsheet which were present in the input section. Requested further changes of the software from the developers.

n) After the issues were sorted out, a final discussion was conducted with the developer team and the academic supervisor. The academic supervisor was satisfied with the working of the software and agreed to the starting of the data collection procedure.

Figure S1-S12 show the snapshots of the ASPIRE 2 registry database and table S1 shows the differences between ASPIRE 1 and ASPIRE 2 registry databases.

Methods

Consecutive treatment naïve patients with newly diagnosed CTEPH at the Sheffield Pulmonary Vascular Disease Unit between 1st January 2001 and 30th November 2014 were identified and followed up until the 30th of November 2015.

Data pertaining to baseline characteristics, treatment and follow-up of the patients were collected from hospital records and departmental databases. Baseline characteristics included demographics, presenting symptoms, past medical history and investigations including blood testing, pulmonary function, exercise testing, right heart catheter studies, and imaging which included isotope perfusion scanning, computer tomography pulmonary angiography, magnetic resonance angiography, cardiac magnetic resonance imaging and digital subtraction angiography (DSA). Data on PH specific targeted therapy, PEA surgery and anticoagulation were also collected. Follow-up data included World Health Organization functional class, incremental shuttle walk distance, pulmonary function test, right heart catheter studies and cardiac magnetic resonance imaging.

The diagnosis of CTEPH was based on findings obtained after at least 3 months of anti-coagulation and required a mean pulmonary arterial pressure ≥25 mm Hg at rest and at least one segmental perfusion defect detected by perfusion lung scan or pulmonary artery obstruction seen by MDCT angiography or conventional pulmonary angiography with other causes of PH excluded (Galie et al., 2015). Patients were further classified into a) surgical-operated group, consisting of patients with surgically accessible disease who underwent PEA surgery, b) surgical-not-operated group, consisting of patients with surgically accessible disease who did not undergo PEA surgery and c) non–surgical group, consisting of patients with inoperable disease due to disease distribution. The surgical but not operated group was further sub-

classified into five categories based on the reasons for the surgery not being performed. These included patients' choice, being unfit for surgery (due to age and co-morbidities), awaiting surgery at the time of census, chronic thromboembolic disease (CTED) with co-morbidities where symptoms may be related to other factors in addition to CTED, and reason for decision not clear. Patients awaiting surgery at the time of census were excluded from the analyses.

Suitability for PEA surgery was assessed by a review of clinical and radiological information by the surgical multidisciplinary team at Papworth Hospital, Cambridge. This team included pulmonary vascular radiologists, physicians and nurses together with PEA surgeons. Data regarding clinical status, standard investigations including RHC and the appearance of at least two radiological investigations were considered when deciding operability. Patients who were deemed to have potentially operable disease were invited to meet the surgical team at Papworth. Only after a face-to-face surgical review were patients asked to make a decision regarding surgery.

The date at which the patient was first diagnosed as having CTEPH was recorded as the date of the first right heart catheterization. All the patients were followed up until death or the census end date of 30th November 2015. Mortality data was obtained from the hospital records at this date. Ethical approval was granted for this study (REC Reference number 06/Q2308/8). This study was registered in ClinicalTrials.gov (ID: NCT02565030, dated 28/09/2015).

Statistical analysis

Descriptive data was presented using mean and standard deviation (SD). Comparison between groups was made using t-test and ANOVA (with Bonferroni corrections for three groups) for continuous data and Chi-squared tests for categorical data. Survival was assessed by the Kaplan-Meier analysis method. Further comparisons between two groups were performed using log-rank test. A total of 74 variables in CTEPH-whole cohort, 72 variables in CTEPH-surgical-operated, 71 variables each in CTEPH-surgical-not-operated and CTEPH-non-surgical disease

distribution group were identified based on previous literature and expert opinion (table S2) (Delcroix et al., 2016) (Condliffe et al., 2008). Prognostic variables were assessed using univariate and multivariate cox regression analysis for survival. After univariate cox regression analysis variables with a p value of < 0.20 with missing data of < 10% were included for the multivariate analysis using forward logistic regression method. A p value of < 0.05 was considered statistically significant. Accuracy of variables was assessed by using receiver operator characteristic (ROC) analysis and area under the curve (AUC). Furthermore, sensitivity, specificity, NPV, and PPV were calculated. The statistical analysis was performed using SPSS software (IBM SPSS statistics version 25) and GraphPad software (Prism).

Table 4: Registries in chronic thromboembolic pulmonary hypertension

Registry	Type	Follow-up period (Mean)	Diagnostic group	Number of cases	Survival at 1 year	Survival at 3 years	Survival at 5 years	Survival at 10years	Predictors of survival	Author-year of Publication
Poland	Retrospective data	1991-1997	Medically treated CTEPH (anticoagulation)	49					mPAP, COPD, severe exercise intolerance	(Lewczuk et al., 2001)
USA (San Diego)	Retrospective	1970-2002	CTEPH undergoing PEA	1500					Preoperative PVR (>1000 dynes/sec/cm-5 Postoperative PVR(>500 dynes/sec/cm-5)	(Jamieson SW, 2003)
UK (Cambridge)	Retrospective	1994-2005	CTEPH (proximal and distal) and IPAH	179	98.5% (Proximal CTEPH) 77% (Distal CTEPH) 86% (IPAH)	97% (Proximal CTEPH) 53% (Distal CTEPH) 60% (IPAH)	97% (Proximal CTEPH)			(Suntharalingam et al., 2007)
Italy	Prospective	1994-2006	CTEPH undergoing PEA	157			84%		Postoperative WHO FC III/IV, unsuccessful PEA, higher preoperative mPAP, PVR and lower Cardiac Output and PaO2	(Corsico et al., 2008)

Registry	Type	Follow-up period (Mean)	Diagnostic group	Number of cases	Survival at 1 year	Survival at 3 year	Survival at 5 years	Survival at 10 years	Predictors of survival	Author-year of Publication
UK	Retrospective	2001-2006	Surgical (PEA group) Non-surgical(distal) group	469	88% (PEA-surgical group) 82% (non-surgical group)	76% (PEA-surgical group) 70% (non-surgical group)			Surgical- exercise capacity and gas transfer Non-surgical- cardiac index & exercise capacity	(Condliffe et al., 2008, Condliffe et al., 2009)
Netherland	Retrospective	1999-2008	In-operable CTEPH	84	93%	78%	68%		6MWD	(Saouti et al., 2009b)
USA (San Diego)	Retrospective	1999-2010	PEA	2700			82%	75%	Preoperative PVR (>1000 dynes/sec/cm-5 Postoperative PVR (>500 dynes/sec/cm-5)	(Madani et al., 2012)
Austria	Retrospective	1994-2010	PEA	110	92%	89%	85%	61%	Immediate postoperative PVR≥ dynes/sec/cm-5	(Skoro-Sajer et al., 2014)

Registry	Type	Follow-up period (Mean)	Diagnostic group	Number of cases	Survival at 1 year	Survival at 3 years	Survival at 5 years	Survival at 10 years	Predictors of survival	Author-year of Publication
UK	Retrospective	1997-2012	PEA	880	86%	84%	79%	72%	Postoperative mPAP (3-6 months ≥ 38mmHg) Postoperative PVR (3-6 months) ≥ 425 dynes/sec/cm-5	(Cannon et al., 2016)
International CTEPH registry	Prospective	2007-2009	PEA group Non-PEA group	679	93% (PEA group) 88% (Non-PEA group)	91% (PEA group) 79% (Non-PEA group)	81% (PEA group) 70% (Non-PEA group)		PEA group-NYHA class VI, RAP, h/o cancer, bridging therapy, PH post PEA, surgical complications and additional cardiac procedures Non-PEA Group- NYHA class VI, RAP, h/o cancer, CAD, LVF and COPD	(Pepke-Zaba et al., 2011) (Delcroix et al., 2016)

Registry	Type	Follow-up period (Mean)	Diagnostic group	Number of cases	Survival at 1 year	Survival at 3 years	Survival at 5 years	Survival at 10 years	Predictors of survival	Author-year of Publication
Spain	Prospective	2006-2013	PEA group & Non-PEA group	391	97% (PEA group) 93% (Non-PEA group)	90% (PEA group) 81% (Non-PEA group)	86% (PEA group) 65% (Non-PEA group)		Whole group - 6MWD, Pericardial effusion, Cardiac output & PEA PEA group- Pericardial effusion and Cardiac output. Non-PEA group- 6MWD, Pericardial effusion, Cardiac Output & Proximal lesion	(Escribano-Subias et al., 2016)
Austria	Prospective	1992-2013	PEA	214	91%				Risk factor for 30-day mortality- high PVR, NYHA FC IV, and low CI. Risk factor for mortality in first 6 months after PEA- high PVR, Reduced CI and old age and post operative classification CTEPH type IV	(Nierlich et al., 2016)
Japan (Tokyo)	Retrospective	2009-2016	CTEPH undergoing BPA	170	99%	98%	95%			(Inami et al., 2016)

Registry	Type	Follow-up period (Mean)	Diagnostic group	Number of cases	Survival at 1 year	Survival at 3 years	Survival at 5 years	Survival at 10 years	Predictors of survival	Author-year of Publication
Japan (Chiba)	Retrospective	1986-2011	CTEPH	214			61% Medically treated in-operable CTEPH 90% (PEA group)		Medically treated -in-operable CTEPH (PH therapy, Kco and PVR) PEA group- Kco	(Suda et al., 2017)
Denmark	Retrospective	1994-2016	CTEPH undergoing PEA	239		84%	77%	62%		(Korsholm et al., 2017)
Europe	Prospective	2009-2017	Non-PEA group & PH post PEA on PH specific targeted therapy	561	99% (Low risk) 95% (Intermediate risk) 76% (High risk)		88% (Low risk) 62% (Intermediate risk) 33% (High risk)		WHO FC & BNP/NT-ProBNP	(Delcroix et al., 2018)
France	Retrospective	2005-2009	CTEPH-operated	383	93%	92%			Age and PVR	(Tromeur et al., 2018)

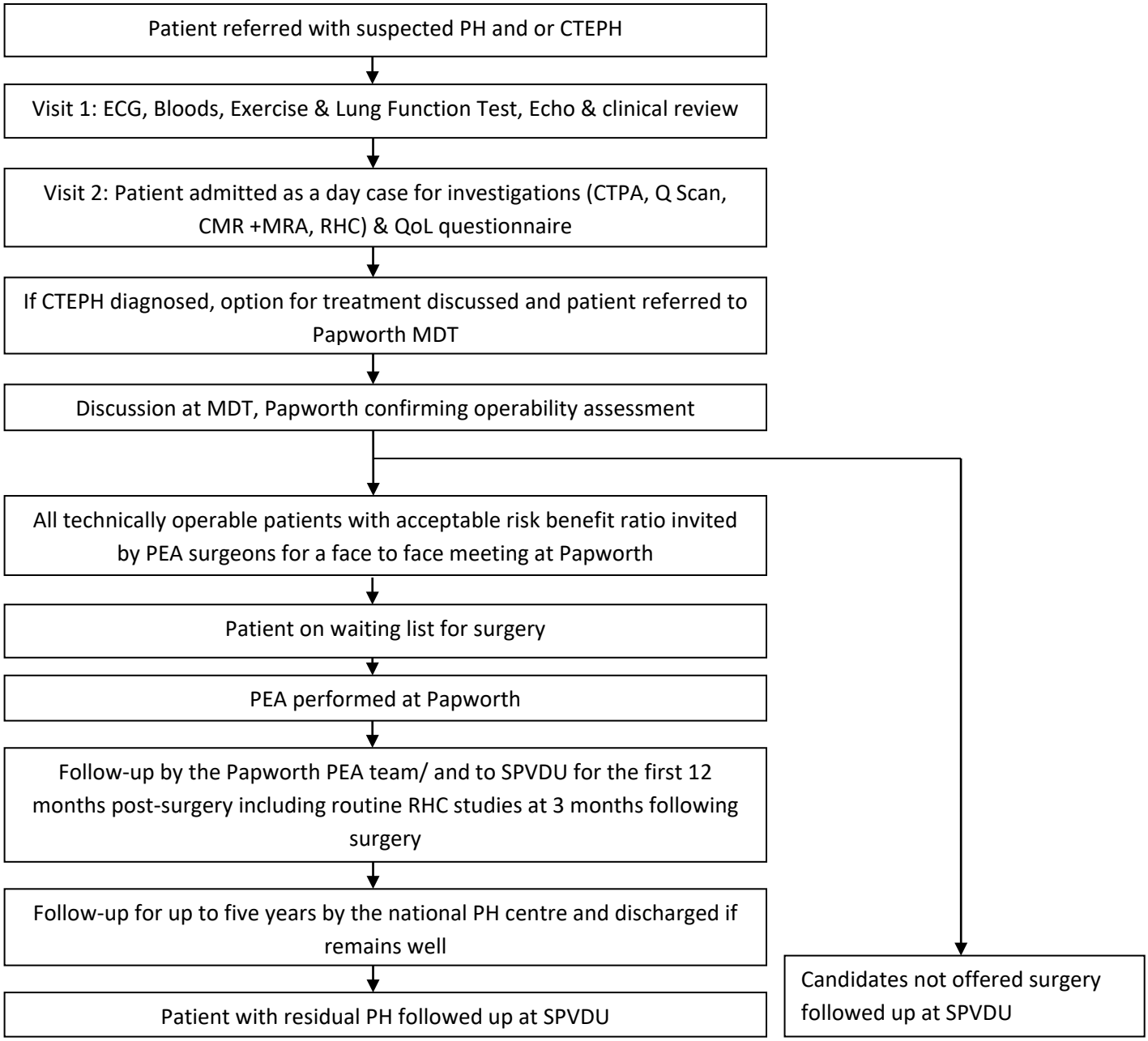
Definition of abbreviations; CTEPH = chronic thromboembolic pulmonary hypertension; mPAP = mean pulmonary artery pressure; COPD = chronic obstructive pulmonary disease; PEA = pulmonary endarterectomy; PVR = pulmonary vascular resistance; IPAH = idiopathic pulmonary arterial hypertension; WHO FC = World Health Organisation functional class; PaO_2 = partial pressure of oxygen(arterial); 6MWD = 6 minute walk distance; NYHA = New York heart association; RAP = right atrial pressure; H/O = history of; PH = pulmonary hypertension; CAD = coronary artery disease; LVF = left ventricular failure; CI = cardiac index; BPA = balloon pulmonary angioplasty; Kco = carbon monoxide transfer co-efficient; BNP = brain natriuretic peptide;

Table 5: Follow-up at the national PEA centre following pulmonary endarterectomy (Ponnaberanam A., 2015, Taboada et al., 2014)

Time following surgery	Location	Follow-up Investigations
3-6 months	Papworth Hospital, Cambridge	CAMPHOR QoL, WHO FC, Blood tests, ECG, Chest radiograph, Echo, PFT, 6MWT, RHC, CTPA and or MRI
12 months	Papworth Hospital, Cambridge or local PH centre	As day case or in-patient based on the investigations required (usually all the above and RHC in patients with elevated PAP at initial 3-6-month post-op RHC)

Definition of abbreviations; QoL = quality of life; WHO FC = World Health Organization functional class; PTE = pulmonary thromboendarterectomy; ECG = electrocardiogram; PFT = pulmonary function test; 6MWT = six-minute walk test; RHC = right heart catheterization; CTPA = computed tomography pulmonary angiogram; MRI = magnetic resonance imaging;

Figure 6: Patient pathway in the management of CTEPH at the SPVDU



Definitions of abbreviations; PH = pulmonary hypertension; CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiogram; Q Scan = perfusion scan; CMR = cardiac MR; MRA = magnetic resonance angiography; RHC = right heart catheterization; QoL = quality of life; National PEA MDT consists of pulmonary vascular physicians, interventional cardiologists, radiologists, PTE specialist nurses and PEA surgeons.

Chapter 3: Long term outcome, prognostic and aetiological factors and the impact of patient choice on survival in chronic thromboembolic pulmonary hypertension

(Quadery R et al, European Respiratory Journal 2018)

Abstract

Background

Pulmonary endarterectomy (PEA) is the gold standard treatment for operable chronic thromboembolic pulmonary hypertension (CTEPH). However, a proportion of patients with operable disease decline surgery. There are currently no published data on this patient group. The aim of this study was to identify outcomes and prognostic factors in a large cohort of consecutive patients with CTEPH.

Methods

Data was collected for consecutive, treatment-naïve CTEPH patients between 2001-2014 identified from the ASPIRE registry.

Results

Of 550 CTEPH patients (age 63±15 years, follow-up 4±3 years), 49% underwent surgery, 32% had technically operable disease and did not undergo surgery (including patient choice n=72, unfit for surgery n=63) and 19% had inoperable disease due to disease distribution. Five-year-survival was superior in patients undergoing PEA (83%) versus technically operable disease who did not undergo surgery (53%) and inoperable due to disease distribution (59%), $p<0.001$. Survival was superior in patients following PEA compared to those offered but declining surgery (55%), $p<0.001$. In patients offered PEA, independent prognostic factors included mixed venous oxygen saturation, gas transfer and patient decision to proceed to surgery.

Conclusions

Outcomes in CTEPH following PEA are excellent and superior to patients declining surgery and strongly favour consideration of a surgical intervention in eligible patients.

This study was registered with Clinicaltrials.gov, registration number NCT02565030.

Introduction

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a potentially curable form of pulmonary hypertension (PH) (Kim et al., 2013). It may follow an acute episode of pulmonary embolism (PE) (Lang et al., 2013) (Pepke-Zaba et al., 2013b) but can present as unexplained PH with no previous history of venous thromboembolism (VTE) (Hoeper et al., 2006, Humbert M, 2010, Lang, 2004). CTEPH occurs as a consequence of failure of clot resolution and secondary pulmonary arterial vasculopathy leading to the development of PH, right ventricular dysfunction and ultimately death (Humbert M, 2010, Moser and Braunwald, 1973). Over the past 20 years the treatment of CTEPH has evolved to include pulmonary endarterectomy (PEA) in operable cases (Jamieson SW, 2003) and PH specific therapy for inoperable disease (Cannon JE, 2013, Ghofrani et al., 2013, Ghofrani et al., 2017, Jais et al., 2008, Reichenberger et al., 2007, Simonneau et al., 2016, Suntharalingam et al., 2008). Balloon pulmonary angioplasty is emerging as a potential treatment option in selected patients with inoperable disease (2018) (Kim et al., 2013, Feinstein et al., 2001, Galie et al., 2015, Mizoguchi et al., 2012, Inami et al., 2016).

Pulmonary endarterectomy is currently considered the treatment of choice in patients with operable CTEPH and is associated with excellent symptomatic benefit and long-term survival (Bonderman et al., 2007, Galie et al., 2015, Konstantinides, 2014) with 10-year survival of 72-75% (Cannon et al., 2016, Madani et al., 2012). Historical studies in patients treated with anticoagulation alone reported a 5-year survival of as low as 10% in patients with a mPAP of > 50mmHg (Lewczuk et al., 2001, Riedel M, 1982). However, subsequent large registries have shown significant improvements in outcome in a heterogeneous group of non-operated patients (Delcroix et al., 2016, Escribano-Subias et al., 2016). Patients with CTEPH may be deemed inoperable where the pulmonary vascular resistance is deemed to be out of proportion to the degree of surgically accessible obstruction in the pulmonary vasculature (Delcroix et al., 2016, Pepke-Zaba et al., 2011). A significant proportion of patients who have

technically operable disease do not undergo surgery for a variety of reasons including comorbidities and patient choice (Delcroix et al., 2016, Escribano-Subias et al., 2016, Pepke-Zaba et al., 2011, Hurdman et al., 2012, Bunclark, 2017, Gall et al., 2017). To date, there are only limited data on the clinical course and rationale for treatment decisions in this patient group. In particular, there is very limited data on patients with technically operable disease who have declined surgery.

The aim of the current study was to provide data to help inform patient choice by identifying outcomes and prognostic factors in a large cohort of consecutive patients with CTEPH.

Methods

The methods are described previously in chapter 2.

Statistical Analysis

The statistical analyses are described previously in chapter 2.

Results

Five hundred and fifty patients with CTEPH (mean age 63±15 years, 50% female) were identified. A flow chart showing the classification with detailed breakdown of patients is shown in figure 7. The number of patients newly diagnosed with CTEPH at the study centre each year between 2001 and 2014 is shown in figure 8.

Patient characteristics

CTEPH (whole cohort)

Baseline characteristics for the major groups are summarised in table 6. There was excellent data completeness with data on lung function testing, exercise testing and imaging available in 94%, 94% and 93% of patients respectively. Right heart catheterisation was performed in all patients. Survival data up to the census end date was available for all patients. The most

common presenting symptoms were breathlessness (98%), ankle swelling (38%), pre-syncope (27%) and chest pain (19%). There was no significant difference in symptoms or duration of symptoms prior to diagnosis between patients with a non-surgical disease distribution and those with technically operable disease (both undergoing not undergoing surgery). Ninety-five percent of patients were white with no significant difference in ethnicity between the CTEPH groups. With respect to anticoagulation, 90% of the patients received a vitamin K antagonist, 4.5% received anti-Xa oral anticoagulants and 5% low molecular weight heparin while 0.5% did not receive any anticoagulation therapy. Seventy-six percent of patients received PH specific therapy, of whom 315 received PDE-5i monotherapy, 49 endothelin receptor antagonist monotherapy, 22 prostanoid monotherapy, 18 combination therapy with a PDE-5i and endothelin receptor antagonist and 12 combination therapy with a PDE-5i and prostanoid. No patients received riociguat (table 7).

CTEPH - operated

Patients with CTEPH who underwent surgery were younger with a male predominance, better exercise capacity, and gas transfer as compared to patients in the other groups (table 6). The mean waiting time from date of diagnosis to surgery at the UK PEA centre was 290±175 days. Seventy-four percent received bridging therapy, of whom 74% received monotherapy with phosphodiesterase-5-inhibitors. Bridging therapy commenced at diagnosis and therefore did not lead to delay in referral for surgical consideration or time to surgery (table 8).

CTEPH - declined surgery (patient choice)

Compared with patients undergoing PEA, patients who declined surgery were older, more likely to be female, had more comorbidities and lower exercise capacity ($p < 0.05$, table 9).

CTEPH – technically operable not offered surgery (unfit for surgery, other contributors to symptoms in addition to clot burden)

Patients who were unfit for surgery had worse exercise capacity, lower D_{LCO}, were more likely to be current smokers and had a higher prevalence of COPD than other technically operable patients not undergoing surgery. Patients with other contributors to symptoms in addition to clot burden (where the risk of surgery was felt to outweigh the benefit) had milder pulmonary haemodynamics and a better exercise capacity than the other 2 sub-groups. The baseline characteristics of these patients are described in further detail in table 10.

CTEP - non-surgical disease distribution

History of VTE was less common in patients with non-surgical disease. However, history of thyroid disease and splenectomy was significantly more common in this sub-group compared to patients undergoing PEA (table 6).

Outcomes

CTEPH (whole cohort)

During a mean follow-up of 4±3 years, 182 (32%) patients died: 51 in the CTEPH surgically operated group, 76 in the CTEPH technically operable but not operated group and 49 in the CTEPH non-surgical group. Estimated 1, 3 and 5-year survival from date of right heart catheterisation was superior in the CTEPH operated group (97%, 87% and 83%) compared to both the CTEPH technically operable but not operated group (87%, 63% and 53%) and CTEPH non-surgical group (92%, 75% and 59%); $p<0.001$, (figure 9).

CTEPH - operated

Persistent PH (as defined by mPAP ≥ 25 mmHg) post-PEA surgery was found in 108 (40%) patients in this study. There was no significant difference in long term survival between the patients who developed PH post-PEA versus the patients who did not develop PH post-PEA

(p=0.288, figure 10). However, those with a post-operative PVR above the median (3 WU) had a worse prognosis following surgery (p=0.013, figure 11). There was no significant difference in survival between patients who received bridging therapy versus patients who did not receive bridging therapy prior to surgery (3-year survival 86% versus 90%, p=0.447, figure 12) as per univariate analysis (HR 0.772, CI 0.39-1.51, p = 0.448), although those who received bridging therapy had more severe pulmonary haemodynamics at diagnosis (mPAP 50 mmHg versus 40 mmHg, PVR 8.8 WU versus 5 WU, p-value both <0.001) (table 8).

CTEPH - declined surgery (patients' choice)

The estimated 5-year survival of patients who declined surgery was significantly worse than those undergoing PEA (55% versus 83%, p<0.001, figure 13A). The impact of age on long term outcome in patients offered surgery is shown in figure 13B-D. A survival benefit was seen in patients both under (p=0.036) and over 60 yrs of age (p<0.001). In more elderly patients above 70 years of age a trend in favour of surgery was observed (p=0.056).

CTEPH – technically operable not offered surgery (unfit for surgery, other contributors to symptoms in addition to clot burden)

Patients deemed unfit for surgery had a significantly worse survival than patients who were offered surgery but declined, who in turn had a significantly worse survival than patients with other contributors to symptoms in addition to clot burden (p<0.05, figure 14). Patients with other contributors to symptoms in addition to clot burden had milder pulmonary haemodynamics (table 11) and similar overall survival (p = 0.281, figure 15) as compared to patients who underwent surgery.

Prognostic indicators

CTEPH (whole cohort)

Univariate analysis of the whole cohort identified a number of predictors of outcome (table 12). Independent predictors of mortality identified from multivariate analysis were: pulmonary endarterectomy (HR 0.38, confidence interval (CI) 0.23-0.63), D_{LCO} (HR 0.59, CI 0.46-0.74), mixed venous oxygen saturation (SvO_2) (HR 0.71, CI 0.57-0.87), history of cancer (HR 2.24, CI 1.28-3.95), chronic kidney disease (HR 2.20, CI 1.22-4.71 age (HR 1.39, CI 1.06-1.80).

CTEPH - offered surgery

Univariate analysis of the CTEPH-offered surgery group identified several predictors of outcome (table 13). Four independent predictors of survival were identified in the combined group of patients offered surgery: patient choice (HR 3.64, CI 1.95-6.81), SvO_2 (HR 0.66, CI 0.49-0.89), D_{LCO} (HR 0.67, CI 0.47-0.95) and the presence of coronary artery disease (HR 2.34, CI 1.11-4.96, table 13).

CTEPH – surgical- operated

Univariate analysis of the CTEPH - surgical-operated group similarly identified a number of predictors of outcome (table 14). Independent predictors of survival from multivariate analysis were age (HR 1.65, CI 1.12-2.42), SvO_2 (HR 0.68, CI 0.49-0.94) and ankle swelling (HR 2.44, CI 1.22-4.87). In addition, it was seen that in this group of patients the waiting time from diagnosis to surgery did not affect survival (figure 16).

CTEPH - declined surgery (patients' choice)

Receiver operator curve analysis for prediction of 3-year mortality was performed for the 3 continuous prognostic variables identified at univariate analysis (table 15 and figure 17): D_{LCO} (AUC 0.87), RAP (AUC 0.81) and SvO_2 (AUC 0.85). Using median thresholds of D_{LCO} 62%, RAP 11 mmHg, and SvO_2 62% the sensitivity, specificity, positive predictive and negative

predictive values for predicting 3-year mortality were calculated as 100%, 63%, 31% and 100%; 80%, 70%, 32% and 95%; and 90%, 60%, 30% and 97%, respectively. Kaplan-Meier estimates of survival in this group using the same variables (D_{LCO}, RAP and SvO_2) were also significant (figure 18).

CTEPH - technically operable not operated

Predictors identified in the univariate analysis included age, WHO FC, exercise capacity, pulmonary haemodynamics and co-morbidities (table 16). Univariate and multivariate analyses for each of the 3 sub-groups are shown in table 17. Independent predictors of outcome were SvO_2 (HR 0.53, CI 0.38-0.76), D_{LCO} (HR 0.54, CI 0.38-0.75), and cancer (HR 4.10, CI 2.02-8.37). In those who declined surgery, SvO_2 (HR 0.24, CI 0.12-0.51) was an independent predictor of survival, whilst in those unfit for surgery exercise capacity (HR 0.41, CI 0.21-0.79), comorbidities (cancer (HR 8.77, CI 2.76-27.81), and CKD (HR 6.98, CI 1.96-24.89), independently predicted outcome. In patients with other contributors to symptoms in addition to clot burden, cancer (HR 9.93, CI 1.98-49.85) was an independent predictor of outcome.

CTEPH - non-surgical disease distribution

Univariate analysis of the CTEPH - non-surgical disease distribution group also identified few predictors of outcome (table 18). Independent predictors of survival from multivariate analysis were PVR (HR 1.44, CI 1.02-2.04) and D_{LCO} (HR 0.39, CI 0.26-0.58).

Discussion

To my knowledge this is the first study that primarily focuses on patients with technically operable CTEPH but did not undergo PEA. Patients' choice, lack of fitness for surgery and the presence of other contributors to symptoms in addition to clot burden were the commonest reasons for patients not undergoing surgery whilst pulmonary haemodynamic severity, D_{LCO} and comorbidities were independent predictors of survival. In addition, in a large cohort of

consecutive patients with CTEPH we have shown that long-term survival of patients undergoing PEA is excellent and superior to patients declining surgery, strongly favouring consideration of a surgical intervention in eligible patients.

CTEPH - whole cohort

Pulmonary endarterectomy is considered the treatment of choice for suitable patients with CTEPH and is thought to provide the best prospect of improved quality and quantity of life (Bonderman et al., 2007, Galie et al., 2015, Konstantinides, 2014). This study, conducted in a large cohort of *consecutive* patients with CTEPH, confirms the results of the international CTEPH registry that PEA is an independent predictor of survival (Delcroix et al., 2016). In operated patients it was associated with an excellent long-term outcome with an estimated 5-year survival of 83%, similar to data from the International (Delcroix et al., 2016), Austrian (Nierlich et al., 2016, Skoro-Sajer et al., 2014) Spanish (Escribano-Subias et al., 2016), Italian (Corsico et al., 2008) and Dutch CTEPH registries (Saouti et al., 2009b). Although 482 patients (81%) had technically operable disease distribution, despite the proven benefits of PEA only 272 (49% of the total cohort) underwent surgery. Previous registries reported similar proportions of patients who underwent PEA but provided only limited data on reasons for not undergoing surgery and predictors of long term outcome (Delcroix et al., 2016, Saouti et al., 2009b, Condliffe et al., 2008).

CTEPH – technically operable not operated

One-hundred and seventy-six (39% of patients with technically operable disease) did not undergo surgery due to: patient choice (n=72), concerns regarding fitness to undergo surgery (n=63) or having other contributors to symptoms in addition to clot burden (n=31) where the benefits of surgery were felt to be minimal. The 5-year survival in patients with technically accessible disease not undergoing surgery was 53%, significantly better than historical studies of patients with CTEPH treated with anticoagulation alone (Lewczuk et al., 2001, Riedel M, 1982). Survival was related to the rationale underpinning the treatment decision with those

declining surgery having a superior survival to those who were deemed unfit for surgery. Not only did markers of disease severity such as SvO_2 and D_{LCO} independently predict survival but also the presence of comorbidities, emphasising the impact of conditions out with the pulmonary vasculature when making treatment decisions.

CTEPH - declined surgery (patients' choice)

The proportion of patients with technically operable disease who were offered surgery (n=344) but declined (n=72, 21%) is larger than previously noted in other registries and may reflect the consecutively-enrolled nature of my study (Delcroix et al., 2016, Saouti et al., 2009b, Condliffe et al., 2008). These data highlight the importance of patients being referred for assessment and counselling by a PEA surgeon and experienced multi-professional team. In patients who declined surgery, the severity of pulmonary haemodynamics and D_{LCO} predicted outcome, with median thresholds for D_{LCO}, right atrial pressure, and SvO_2 having negative predictive values for 3-year mortality >95%. For a selected cohort of patients, who, despite counselling decline surgery this information may be useful, although it must also be emphasised that quality of life benefits in the majority of patients are greater with surgery (Thakrar et al., 2013, Genta et al., 2005). In contrast, patients with severe haemodynamics assessed to be good surgical candidates may find data highlighting a poor prognosis in the absence of a surgical intervention an aid to decision-making.

This study has demonstrated a significantly superior survival in patients with CTEPH who were offered surgery and underwent PEA compared to those who declined. Although patients declining surgery were older, with a poorer exercise capacity and more comorbidities, declining surgery due to patients' choice was an independent predictor of a worse outcome i.e. even when important other factors such as patient age and comorbidities were taken into account patients' choice to decline surgery predicted a significantly worse outcome. In patients who declined compared to those who underwent surgery, there was a female predominance (Hurdman et al., 2012) and gender specific factors related to risk-taking may play a role

(Harris, 2006). Given the findings of this study and the benefit of PEA more work is required to understand factors underlying decisions to decline surgery.

Unfit for surgery

In expert hands PEA has a perioperative mortality of <5% and offers the best chance of longer term survival, but requires careful assessment of risks versus benefits for individual patients (Madani et al., 2012, Delcroix et al., 2016). A total of 63 patients (14% of those with technically operable disease) were deemed unfit for surgery by the MDT. These patients had a significantly poorer survival than those declining surgery. Alternative interventions to surgery such as balloon pulmonary angioplasty may appear attractive in these patients, but the presence of significant comorbidities may be primary determinants of survival. A meticulous assessment balancing the potential symptomatic benefit versus the risks of such interventions is therefore paramount where mortality benefit is not clear.

CTEPH - non-surgical disease distribution

Nineteen percent of all patients were deemed to have non-surgical disease distribution. This proportion is similar to the International CTEPH registry (20%) (Delcroix et al., 2016) but less than the UK (32%) (Condliffe et al., 2008) and Dutch (26%) (Saouti et al., 2009a) registries. This may reflect an increasing willingness amongst surgeons to operate on patients with disease that would previously have been considered too distal to benefit from surgery. Indeed a number of centres have shown that outcomes in patients with Type 3 disease (more distal) in expert hands are now similar to more proximal disease (Type 1 and 2) (Madani et al., 2012) (D'Armini et al., 2014). I noted a female predominance, an increased incidence of thyroid disease and splenectomy and reduced incidence of VTE in this group (table 5) in keeping with previous reports (Corsico et al., 2008).

CTEPH - surgical operated: timing of surgery and pulmonary vasodilator therapy

The mean time from diagnosis to PEA surgery was 290±175 days, longer than previously reported studies (Delcroix et al., 2016, Skoro-Sajer et al., 2014, Condliffe et al., 2008, Mayer et

al., 2011) but in line with waiting times for surgery in the UK during the duration of this study (Gibbs, 2017) although, UK waiting times are now falling (Gibbs, 2018). In keeping with data from the International CTEPH registry, the duration of delay did not impact on long-term survival (figure 16) (Delcroix et al., 2016). A large number of patients were bridged to PEA with off-label PAH–specific therapies (74%). Although there is no published evidence to support this practice, this may reflect the longer time from referral to surgery in the UK during the study period as compared to that reported in the International CTEPH registry (Delcroix et al., 2016). Importantly, bridging therapy had no effect on time to referral or to surgery (table 8). Patients receiving bridging therapy in the present study had similar haemodynamics to those who received bridging therapy in the International CTEPH registry, while patients who were not bridged to surgery had milder haemodynamics than those in the International registry (table 8) (Delcroix et al., 2016). Importantly, in this study receiving bridging therapy was not associated with adverse outcome at univariate analysis (HR 0.772, CI 0.39-1.51, p = 0.448).

Limitations

This study predates the availability of balloon angioplasty and riociguat therapy in the UK and therefore the impact of these interventions and their potential benefits cannot be assessed. Although patient-specific data were enriched by retrospective case note review and interrogation of databases, this resulted in higher levels of data completeness than in other contemporary registries. Furthermore, the consecutive nature of enrolment in the ASPIRE registry reduces recruitment bias associated with previous non-consecutively enrolled studies. This study provides no data on the reasons for patients declining surgery. Although the results suggest that surgery improves survival in patients with technically operable disease who were offered surgery, patients judged to be unfit for surgery by the MDT and those in whom there were other contributors to symptoms in addition to clot burden were excluded. For the individual patient factors including age and comorbidities will influence outcome following surgery. How these factors influence the patient's decision requires further research.

Conclusion

This study report results from a large consecutively enrolled registry of patients with CTEPH. I have been able to compare characteristics and have also identified predictors of survival in patients who did not undergo surgery despite having technically operable disease. My data has shown that survival of patients undergoing PEA is excellent and superior to patients declining surgery and strongly favours consideration of a surgical intervention in eligible patients. More work is required to understand factors influencing decision making in CTEPH and to ensure that patients are counselled and supported to make informed decisions.

Table 6: Baseline characteristics of patients with CTEPH

	CTEPH whole cohort	CTEPH operated	CTEPH technically operable not operated	CTEPH-non-surgical disease distribution
Number (%)	550 (100)	272 (49)	176 (32)	102 (19)
Age (years)	63 (15)	58 (14) $^{\#, +}$	69 (14) $^{*,\$}$	65 (15) *
Gender (%Female)	50	45 $^{+,\#}$	50*	62*
BMI (kg/m^2)	29 (7)	30 (7)	29 (8)	29 (6)
Duration of symptoms (%, <1 year/1-2 years/2-5 years/>5 years/not clear)	15/38/24/16/8	14/40/27/16/3	17/35/19/14/14	12/33/28/18/9
WHO FC (I/II vs III/IV)	11/89	13/87^{+}	11/89	3/97*
ISWD (m)	189 (177)	232 (185)$^{\#, *}$	142 (157) *	155 (160) *
RAP (mmHg)	11 (5)	11 (5)	11 (6)	12 (5)
mPAP (mmHg)	46 (11)	47 (11) $^{\#}$	43 (11) $^{*, +}$	48 (12) $^{\#}$
CI (L/min/m^2)	2.5 (0.8)	2.5 (0.7)	2.6 (0.8)	2.5 (0.8)
PCWP (mm of Hg)	12 (5)	12 (4)	12 (6)	11 (4)
PVR (Wood Units)	7.7 (4.3)	7.7 (4)	7 (4.6) $^{+}$	8.7 (4.5) $^{\#}$
SvO_2 (%)	61 (8)	61 (8)	61 (9)	61 (9)
FEV_1 (% predicted)	80 (35)	83 (43) $^{\#}$	75 (23) *	80 (24)
D_{LCO} (% predicted)	61 (17)	65 (15) $^{\#}$	55 (19) $^{*,+}$	61 (17)$^{\#}$
History of acute VTE (%)	71	74 $^{+}$	74^{+}	57$^{*, \#}$
IVC filter (%)	3	3	5	1
Thrombophilia (%)	5	6	3	3
History of cancer (%)	11	6 $^{\#,+}$	15*	15*
Smoking (%)	38	38	43	30
Obesity (%)	36	39	32	32
Splenectomy	5	3 $^{+}$	3 $^{+}$	12 $^{*,\#}$
Thyroid disorder (%)	12	8 $^{+}$	14	18 *
V-A shunt/PPM infection (%)	2	2	0	4
IBD (%)	1	1	2	2
CAD (%)	11	10	14	7
LV dysfunction (%)	4	2 $^{\#}$	8 $^{*, +}$	2 $^{\#}$
Valvular heart disease(%)	2	2	2	2
CKD (%)	7	3 $^{\#}$	13 *	6
COPD (%)	19	13 $^{\#}$	30 *	19
PH therapy following diagnosis (%)	76	74^{+}	72^{+}	86$^{*,\#}$

Definition of abbreviations: n = number of patients; BMI = body mass index; WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; mPAP = mean pulmonary arterial pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; FEV_1 = forced expiratory volume in one second; D_{LCO} = diffusing capacity of lung for carbon monoxide; VTE = venous thromboembolism; IVC = inferior vena cava; PE = pulmonary embolism; V-A = ventricular atrial; PPM = permanent pacemaker; IBD = inflammatory bowel disease; CAD = coronary artery disease; LV = left ventricle; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PH = pulmonary hypertension;
Values are mean (standard deviation) or percentage unless otherwise indicated.
*: $p < 0.05$ in comparison to CTEPH-operated.
#: $p < 0.05$ in comparison to CTEPH-technically-operable-not operated.
+: $p < 0.05$ in comparison to CTEPH-non-surgical-disease-distribution.

Table 7: Detailed breakdown of the PH specific targeted therapy used in patients with CTEPH

PH therapy	Number of patients	Percentage
PDE-5i only	315	76
ERA only	49	13
PGI2 only	22	5
PDE-5i+ERA	18	4
PDE-5i+PGI2	12	3

Definition of abbreviations: PH = pulmonary hypertension; PDE-5i = phosphodiesterase 5 inhibitors; ERA = endothelin receptor antagonists; PGI2 = prostacyclin analogues;

Table 8: Baseline characteristics in patients undergoing PEA who received bridging therapy versus those who received no bridging therapy

	Bridging therapy n=200 (74%)	**No bridging therapy n=72 (26%)**	**p-value**
Age	60 (14)	55 (14)	0.014
Gender (%, Female)	44	47	0.672
WHO FC (I/II vs III/IV) %	6/94	35/65	<0.001
ISWD (m)	183 (143)	366 (220)	<0.001
RAP (mmHg)	11 (5)	8 (5)	<0.001
mPAP (mmHg)	50 (10)	40 (11)	<0.001
CI (L/min/m^2)	2.4 (0.6)	2.9 (0.7)	<0.001
PCWP (mmHg)	11 (4)	12 (4)	0.166
PVR (Wood Units)	8.8 (4)	5 (3)	<0.001
SvO_2 (%)	59 (8)	66 (7)	<0.001
D_{LCO} (%)	64 (15)	68 (16)	0.032
H/o VTE (%)	73	74	0.920
H/o Cancer (%)	7	6	0.751
CAD (%)	12	7	0.257
LV dysfunction (%)	1	6	0.026
CKD (%)	3	1	0.448
COPD (%)	15	7	0.088
Time to Surgery (days)	291 (158)	289 (221)	0.965

Definition of abbreviations: n = number of patients; WHO FC=World Health Organization functional class; ISWD= Incremental shuttle walk distance; RAP=right atrial pressure; mPA=mean pulmonary arterial pressure; CI=cardiac index; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; SvO_2=mixed venous oxygen saturation; D_{LCO}= diffusing capacity of lung for carbon monoxide; VTE=venous thromboembolism; CAD=coronary artery disease; LV=left ventricle; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease;
Values are mean (standard deviation) or percentage unless otherwise indicated.
Comparison between continuous variables and categorical variables were made by t-test and Chi squared tests respectively.

Table 9: Baseline characteristics of CTEPH-operated group versus patients who declined surgery (patient choice)

	CTEPH-operated	**CTEPH declined surgery (patient choice)**	**p- value**
Number of patients	272	72	
Age (years)	58 (14)	68 (16)	<0.001
Gender (%, Female)	45	63	0.007
BMI	30 (7)	29 (7)	0.485
WHO FC (I/II Vs II/IV)	13/87	17/83	0.462
Duration of symptoms (<1 year/1-2 years/2-5 years/>5 years/not clear)	14/40/27/16/3	22/38/17/11/13	0.009
ISWD (m)	232 (185)	169 (177)	0.009
RAP (mmHg)	11 (5)	12 (6)	0.192
mPAP (mmHg)	47 (11)	46 (10)	0.360
CI (L/min/m2)	2.5 (0.8)	2.6 (0.8)	0.305
PCWP (mmHg)	12 (4)	12 (5)	0.667
PVR (Wood Units)	7.7 (4)	8 (4)	0.767
SvO_2 (%)	61 (8)	61 (9)	0.610
FEV_1 (% predicted)	83 (43)	82 (21)	0.714
D_{LCO} (% predicted)	65 (15)	61 (17)	0.084
History of VTE (%)	74	69	0.489
History of cancer (%)	6	6	0.827
Smoking (%)	38	35	0.664
Obesity (%)	39	26	0.048
CAD (%)	11	8	0.620
LV dysfunction (%)	2	6	0.131
CKD (%)	3	14	<0.001
COPD (%)	13	17	0.356
PH therapy following diagnosis (%)	74	75	0.849

Definition of abbreviations: n = number of patients; BMI = body mass index; WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; mPAP = mean pulmonary arterial pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; FEV_1 = forced expiratory volume in one second; D_{LCO} (%) = diffusion capacity of lung for carbon monoxide; VTE = venous thromboembolism; CAD = coronary artery disease; LV = left ventricle; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PH = pulmonary hypertension;
Values are mean (standard deviation) or percentage unless otherwise indicated.
Comparison between continuous variables and categorical variables were made by t-test and Chi squared tests respectively.

Table 10: Baseline characteristics in CTEPH-technically-operable-not-operated sub-groups (declined surgery (patient choice), unfit for surgery and CTEPH where symptoms may be related to other factors in addition to clot burden)

	Declined surgery - patient choice	**Unfit for surgery**	**Other contributors to symptoms in addition to clot burden**
Number of patients	72	63	31
Age (years)	68 (16)	70 (12)	69 (12)
Gender (%, Female)	63	41	45
BMI	29 (7)	29 (8)	32 (8)
WHO FC (I/II vs III/IV)	17/83 *	3/97 #	19/81
Duration of symptoms (<1 year/1-2 years/2-5 years/>5 years/not clear)	22/38/17/11/13	11/37/18/21/14	19/36/23/10/7
ISWD (m)	169 (177) *	95 (119) #,+	210 (162) *
RAP (mmHg)	12 (6) +	11 (6)	8 (3) #
mPAP(mmHg)	46 (10) +	46 (10) +	31 (7) #, *
CI (L/min/m2)	2.6 (0.8) +	2.4 (0.7) +	3.3 (0.6) #,*
PCWP (mmHg)	12 (5)	13 (6)	13 (6)
PVR (Wood Units)	8 (4) +	8.5 (5) +	3 (1.4) #
SvO_2 (%)	61 (9) +	59 (9) +	68 (6) #, *
FEV_1 (% predicted)	82 (21) *	66 (22) #, +	81 (23) *
D_{LCO} (% predicted)	61 (17) *	43 (16) #, +	65 (18) *
History of VTE (%)	70	76	90
IVC filter (%)	4	8	0
Thrombophilia (%)	7	2	0
History of cancer (%)	6+	19	32 #
Smoking (%)	35 *	62 #, +	36 *
Obesity (%)	26	30	45
CAD (%)	8	21	13
LV dysfunction (%)	6	13	10
Valvular heart disease (%)	0	3	3
CKD (%)	14	13	10
COPD (%)	17 *	48 #	29
PH therapy following diagnosis (%)	75 *, +	87 #, +	13 #, *

Definition of abbreviations: n = number of patients; BMI = body mass index; WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; mPAP = mean pulmonary arterial pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; FEV_1 = forced expiratory volume in one second; D_{LCO} = diffusing capacity of lung for carbon monoxide; VTE = venous thromboembolism; IVC = inferior vena cava; PE = pulmonary embolism; CAD = coronary artery disease; LV = left ventricle; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PH = pulmonary hypertension;
Values are mean (standard deviation) or percentage unless otherwise indicated.
Mean (standard deviation) or percentage presented.
#: $p < 0.05$ in comparison to CTEPH-technically-operable-not operated (patient choice).
*: $p < 0.05$ in comparison to CTEPH-technically-operable-not-operated (unfit for surgery).
+: $p < 0.05$ in comparison to CTEPH, technically-operable-not operated (other contributors to symptoms in addition to clot burden).

Table 11: Baseline characteristics of CTEPH-operated group versus patients with other contributors to symptoms in addition to clot burden

	CTEPH-operated	**Other contributors to symptoms in addition to clot burden**	**p- value**
Number	272 (49)	31	
Age (years)	58 (14)	69 (12)	<0.001
Gender (%, Female)	45	45	0.943
BMI	30 (7)	32 (8)	0.109
WHO FC (I/II vs III/IV)	13/87	19/81	0.355
Duration of symptoms (<1 year/1-2 years/2-5 years/>5 years/not clear)	14/40/27/16/3	19/36/23/10/7	0.025
ISWD (m)	232 (185)	210 (162)	0.492
RAP (mmHg)	11 (5)	8 (3)	0.020
mPAP(mmHg)	47 (11)	31 (7)	<0.001
CI (L/min/m2)	2.5 (0.7)	3.3 (0.6)	<0.001
PCWP (mmHg)	12 (4)	13 (6)	0.154
PVR (Wood Units)	7.7 (4)	3 (1.4)	<0.001
SvO_2 (%)	61 (8)	68 (6)	<0.001
FEV_1 (% predicted)	83 (43)	81 (23)	0.624
D_{LCO} (% predicted)	65 (15)	65 (18)	0.928
History of VTE (%)	74	90	0.040
IVC filter (%)	3	0	0.366
Thrombophilia (%)	6	0	0.165
History of cancer (%)	6	32	<0.001
Smoking (%)	38	36	0.826
Obesity (%)	36	45	0.504
CAD (%)	10	13	0.654
LV dysfunction (%)	2	10	0.020
Valvular heart disease (%)	2	3	0.599
CKD (%)	3	10	0.036
COPD (%)	13	29	0.012
PH therapy following diagnosis (%)	74	13	<0.001

Definition of abbreviations: n = number of patients; BMI = body mass index; WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; mPAP = mean pulmonary arterial pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; FEV_1 = forced expiratory volume in one second; D_{LCO}= diffusing capacity of lung for carbon monoxide; VTE = venous thromboembolism; IVC = inferior vena cava; PE = pulmonary embolism; CAD = coronary artery disease; LV = left ventricle; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PH = pulmonary hypertension;
Values are mean (standard deviation) or percentage unless otherwise indicated.
Comparison between continuous variables and categorical variables were made by t-test and Chi squared tests respectively.

Table 12: Cox regression survival analysis for CTEPH-whole cohort

		Univariate analysis			Multivariate analysis		
Covariates		**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age*	/15 years	1.68	1.40-2.02	<0.001	1.39	1.06-1.80	0.016
BMI*	/7 kg/m^2	0.82	0.68-0.99	0.046			
WHO FC	I/II or III/IV Ref= I/II	2.20	1.12-4.30	0.021			
ISWD*	/177 m	0.51	0.41-0.63	<0.001			
RAP*	/5 mmHg	1.30	1.14-1.49	<0.001			
CI*	/0.8 L/min/m^2	0.75	0.64-0.88	<0.001			
PVR*	/4.3 Wood Units	1.36	1.16-1.60	<0.001			
SvO_2*	/8%	0.66	0.57-0.76	<0.001	0.71	0.57-0.87	0.001
FEV_1*	/35%	0.65	0.49-0.86	0.002			
D_{LCO}*	/17%	0.52	0.44-0.62	<0.001	0.59	0.46-0.74	<0.001
VTE	ref = absent	0.70	0.51-0.95	0.020			
Cancer	ref = absent	2.33	1.58-3.45	<0.001	2.24	1.28-3.95	0.005
Obesity	ref = absent	0.68	0.49-0.95	0.023			
Thyroid disorders	ref = absent	1.35	0.88-2.06	0.166			
CAD	ref = absent	2.17	1.47-3.18	<0.001			
LVF	ref = absent	1.77	0.86-3.48	0.096			
CKD	ref = absent	2.33	1.44-3.77	0.001	2.20	1.22-4.71	0.021
PEA	ref = not performed	0.31	0.22-0.43	<0.001	0.38	0.23-0.63	<0.001

Data shown for univariate analysis where p < 0.20, 72 variables were imported into univariate analysis.
Definition of abbreviations: ref = reference parameter; BMI = body mass index; WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; mPAP = mean pulmonary arterial pressure; CI = cardiac index; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; FEV_1 = forced expiratory volume in one second; D_{LCO} = diffusing capacity of lung for carbon monoxide; VTE = venous thromboembolism; CAD = coronary artery disease; LVF = left ventricle; failure; CKD = chronic kidney disease;
* These variables are scaled so that the hazard ratio (HR) is the change by one standard deviation (SD).

Table 13: Cox regression survival analysis in CTEPH-technically-operable who were offered surgery (operated group and declined surgery (patient choice) sub-groups)

		Univariate analysis			Multivariate analysis		
Covariates		**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age*	/15 years	1.71	1.30-2.25	<0.001			
WHO FC	I/II or II/IV ref = I/II	3.98	1.25-12.65	0.019			
Cardiac arrhythmia	ref = absent	2.16	1.03-4.53	0.043			
ISWD*	/185 m	0.56	0.41-0.75	<0.001			
RAP*	/6mmHg	1.57	1.25-1.98	<0.001			
PVR*	/4 Wood Units	1.39	1.08-1.78	0.009			
SvO_2*	/8%	0.62	0.49-0.77	<0.001	0.66	0.49-0.89	0.006
D_{LCO}*	/16%	0.56	0.42-0.75	<0.001	0.67	0.47-0.95	0.025
VTE	ref = absent	0.62	0.39-0.98	0.045			
Cancer	ref = absent	1.77	0.85-3.69	0.127			
Obesity	ref = absent	0.55	0.33-10.92	0.024			
Thyroid disorders	ref = absent	1.65	0.87-3.15	0.122			
CAD	ref = absent	2.21	1.24-3.94	0.007	2.34	1.11-4.96	0.026
CKD	ref = absent	1.90	0.82-4.38	0.132			
Patient choice	ref = surgery	2.56	1.57-4.16	<0.001	3.64	1.95-6.81	<0.001

Data shown for univariate analysis where $p < 0.20$, 72 variables were imported into univariate analysis.
Definition of abbreviations: ref = reference parameter; WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; mPAP = mean pulmonary arterial pressure; CI = cardiac index; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; FEV_1 = forced expiratory volume in one second; D_{LCO} = diffusing capacity of lung for carbon monoxide; VTE = venous thromboembolism; CAD = coronary artery disease; CKD = chronic kidney disease; PEA = pulmonary endarterectomy;
* These variables are scaled so that the hazard ratio (HR) is the change by one standard deviation (SD).

Table 14: Cox regression survival analysis of CTEPH-operated group

		Univariate analysis			Multivariate analysis		
Covariates		**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age*	/14 years	1.65	1.19-2.29	0.003	1.65	1.12-2.42	0.011
WHO FC	I/II or III/IV Ref= I/II	2.47	0.77 —7.93	0.130			
ISWD*	/185 m	0.57	0.40-0.82	0.002			
RAP*	/5mmHg	1.35	1.06-1.72	0.017			
mPAP*	/11 mmHg	1.22	0.91-1.62	0.189			
CI*	/0.8 L/min/m^2	0.67	0.45-0.95	0.025			
SvO_2*	/8%	0.66	0.450-0.86	0.002	0.68	0.49-0.94	0.019
FEV_1*	/43%	0.43	0.21-0.86	0.017			
D_{LCO}*	/15%	0.63	0.44-0.89	0.008			
VTE	Ref= absent	0.55	0.31-0.96	0.036			
Cancer	Ref = absent	2.07	0.88-4.86	0.096			
CAD	Ref = absent	2.54	1.30-4.96	0.006			
Ankle swelling	Ref = absent	2.06	1.19-3.57	0.010	2.44	1.22-4.87	0.012
Cardiac arrhythmia	Ref = absent	2.56	1.08-6.07	0.033			

Data shown for univariate analysis where p< 0.20, 75 variables were imported into univariate analysis.
Definition of abbreviations: WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP=right atrial pressure; mPAP = mean pulmonary arterial pressure; CI = cardiac index; SvO_2 = mixed venous oxygen saturation; FEV_1 = forced expiratory volume in one second; D_{LCO} = diffusing capacity of lung for carbon monoxide; VTE = venous thromboembolism; CAD = coronary artery disease;
* These variables are scaled so that the hazard ratio (HR) is the change by one standard deviation (SD).

Table 15: Receiver operating characteristics analysis presenting area under the curve, sensitivity and specificity, positive and negative predictive values in the CTEPH-technically operable-not-operated group (patient choice) at 36 months follow-up

Variable	Threshold (median)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
D_{LCO}	62% (≥ 62% vs < 62%)	0.87	100	63	31	100
RAP	11mmHg (≤ 11mmHg vs > 11 mmHg)	0.81	80	70	32	95
Svo_2	62% (> 62 % vs ≤ 62%)	0.85	90	60	30	97

Definition of abbreviations: AUC = area under curve; D_{LCO} = diffusing capacity of lung for carbon monoxide; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation; PPV = positive predictive value; NPV = negative predictive value;

Table 16: Cox regression survival analysis of CTEPH-technically-operable-not-operated group

		Univariate analysis			Multivariate analysis		
Covariates		**HR**	**95% CI**	**p- value**	**HR**	**95% CI**	**p-value**
Age*	/14 years	1.33	1.02-1.74	0.034			
WHO FC	I/II or III/IV (ref = I/II)	2.80	0.88-8.95	0.081			
ISWD*	/160 m	0.59	0.39-0.79	0.001			
RAP*	/5 mmHg	1.38	1.10-1.73	0.005			
CI*	/0.8L/min/m^2	0.62	0.46-0.82	0.001			
PVR*	/4.6Wood Units	1.59	1.27-2.00	<0.001			
SvO_2*	/9%	0.56	0.44-0.72	<0.001	0.53	0.38-0.76	<0.001
D_{LCO}*	/19 %	0.53	0.39-0.71	<0.001	0.54	0.38-0.75	<0.001
Cancer	Ref=absent	2.98	1.72-5.15	<0.001	4.10	2.02-8.37	<0.001
CAD	Ref=absent	2.18	1.21-3.95	0.010			
CKD	Ref=absent	1.89	1.03-3.48	0.041			

Data shown for univariate analysis where $p < 0.20$, 71 variables were imported into univariate analysis.
Definition of abbreviations: Ref= reference parameter; WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; CI = cardiac index; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; D_{LCO}= diffusing capacity of lung for carbon monoxide; CAD = coronary artery disease; CKD = chronic kidney disease;
* These variables are scaled so that the hazard ratio (HR) is the change by one standard deviation (SD).

Table 17: Cox regression survival analysis for CTEPH-technically-operable-not-operated: patient choice, unfit for surgery and other contributors to symptoms in addition to clot burden sub-groups

Patient choice		**Univariate analysis**			**Multivariate analysis**		
Covariates		**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age*	/16 years	1.40	0.88-2.25	0.160			
WHO FC	I/II or III/IV ref = I/II	27.42	0.27-2732.21	0.158			
ISWD*	/177 m	0.71	0.42-1.19	0.187			
RAP*	/6mmHg	1.83	1.23-2.73	0.003			
CI*	/0.8 L/min/m^2	0.70	0.44-1.10	0.121			
PVR*	/4.25 Wood Units	1.58	1.01-2.49	0.047			
SvO_2*	/9%	0.53	0.34-0.82	0.004	0.24	0.12-0.51	<0.001
D_{LCO}*	/17%	0.52	0.31-0.85	0.009			
Thyroid disorder	ref = absent	1.91	0.74-4.91	0.182			
CAD	ref = absent	2.28	0.67-7.77	0.189			
Unfit for surgery		**Univariate analysis**			**Multivariate analysis**		
Covariates		**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
ISWD*	/114 m	0.65	0.42-0.99	0.046	0.41	0.21-0.79	0.008
RAP*	/6 mmHg	1.27	0.89-1.82	0.185			
CI*	/0.7 L/min/m^2	0.66	0.44-1.01	0.054			
PVR*	/4.94 Wood Units	1.34	0.94-1.88	0.102			
SvO_2*	/9%	0.64	0.44-0.92	0.016			
D_{LCO}*	/17 %	0.75	0.51-1.09	0.133			
Cancer	ref = absent	2.96	1.47-5.97	0.002	8.77	2.76-27.81	<0.001
CKD	ref = absent	2.46	1.06-5.68	0.035	6.98	1.96-24.89	0.003
Other contributors to symptoms in addition to clot burden		**Univariate analysis**			**Multivariate analysis**		
Covariates		**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age*	/12 years	2.53	0.97-6.81	0.067			
WHO FC	I/II or III/IV ref = I/II	4.76	01.06-21.33	0.041			
ISWD*	/162m	0.55	0.23-1.35	0.193			
Cancer	ref = absent	6.63	1.98-49.85	0.005	9.93	1.98-49.85	0.005
LV dysfunction	ref = absent	4.55	0.89-23.08	0.067			

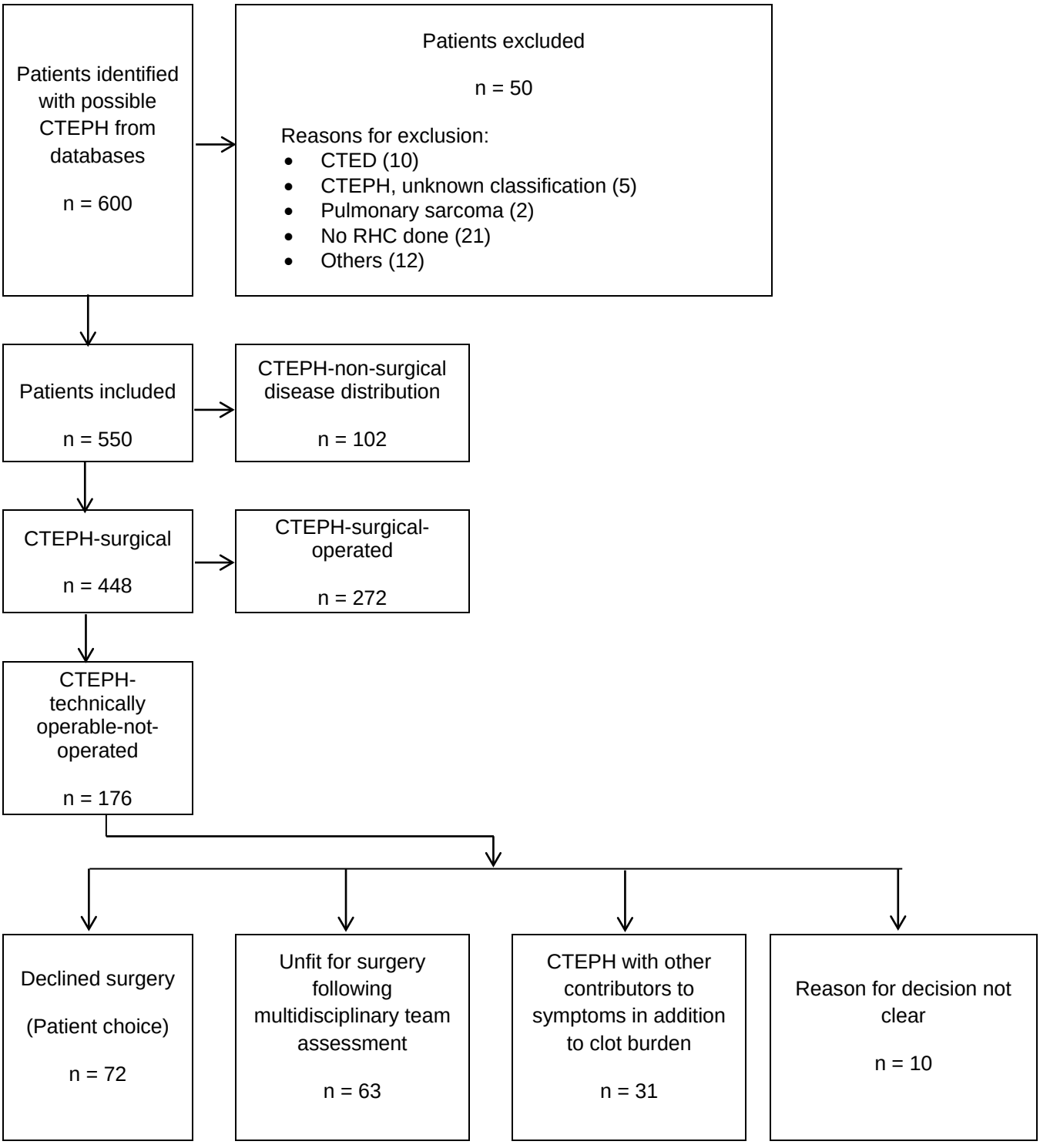
Data shown for univariate analysis where $p < 0.20$, 71 variables were imported into univariate analysis.
Definition of abbreviations: ref = reference parameter; WHO FC = Word Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; CI = cardiac index; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; D_{LCO} = diffusing capacity of lung for carbon monoxide ; CAD = coronary artery disease; CKD = chronic kidney disease; VTE = venous thromboembolism; LV = left ventricular;
* These variables are scaled so that the hazard ratio (HR) is the change by one standard deviation (SD).

Table 18: Cox regression survival analysis of patients with CTEPH-non-surgical disease distribution

		Univariate analysis			Multivariate Analysis		
Covariates		**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age*	/19 years	1.62	0.98-2.66	0.059			
ISWD*	/160m	0.55	0.36-0.85	0.007			
PVR*	4.5 WU	1.27	0.95-1.71	0.101	1.44	1.02-2.04	0.038
SvO_2*	/9%	0.65	0.45-0.91	0.011			
D_{LCO}*	/17%	0.52	0.38-0.72	<0.001	0.39	0.26-0.58	<0.001

Data shown for univariate analysis where $p < 0.20$, 71 variables were imported into univariate analysis.
Definition of abbreviations: ref = reference parameter; WHO FC = World Health Organization functional class;
ISWD = Incremental shuttle walk distance; PVR = pulmonary vascular resistance; SvO2 = mixed venous oxygen saturation; D_{LCO}= diffusing capacity of lung for carbon monoxide; WHO FC = World Health Organization functional class;
* These variables are scaled so that the hazard ratio (HR) is the change by one standard deviation (SD).

Figure 7: Patient cohort flow chart



Definition of abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; CTED = chronic thromboembolic disease; PH = pulmonary hypertension; n = number of patients;

Figure 8: The number of patients newly diagnosed with CTEPH at the study centre each year between 2001 and 2014

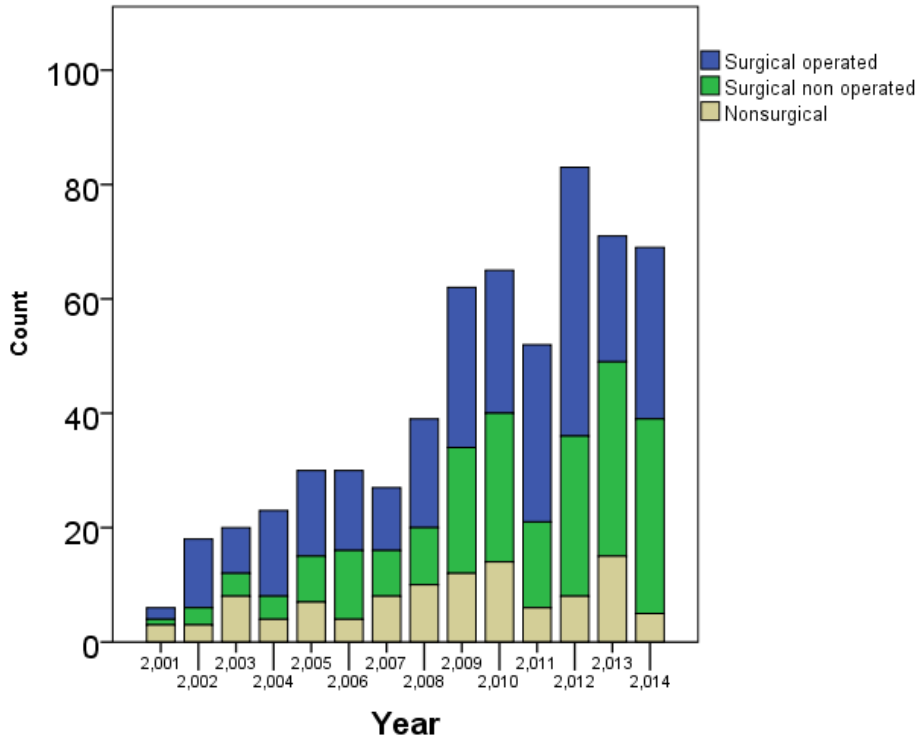
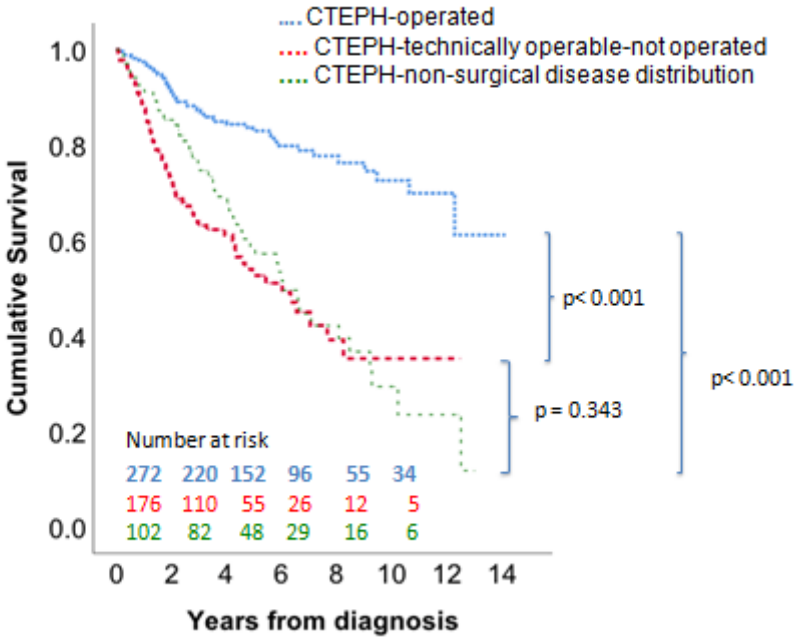
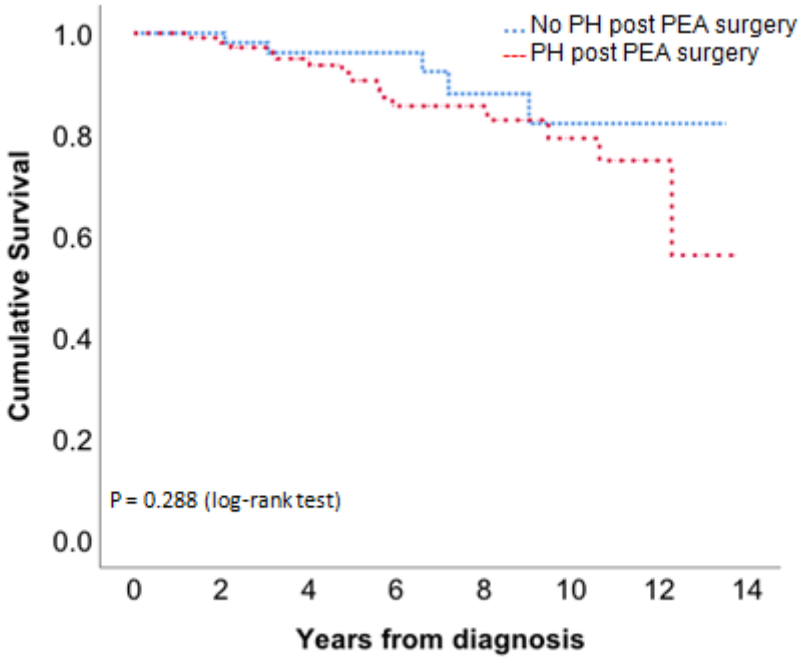


Figure 9: Kaplan-Meier estimates of survival from date of diagnosis in CTEPH- operated, CTEPH-technically-operable-not-operated and CTEPH-non-surgical patients



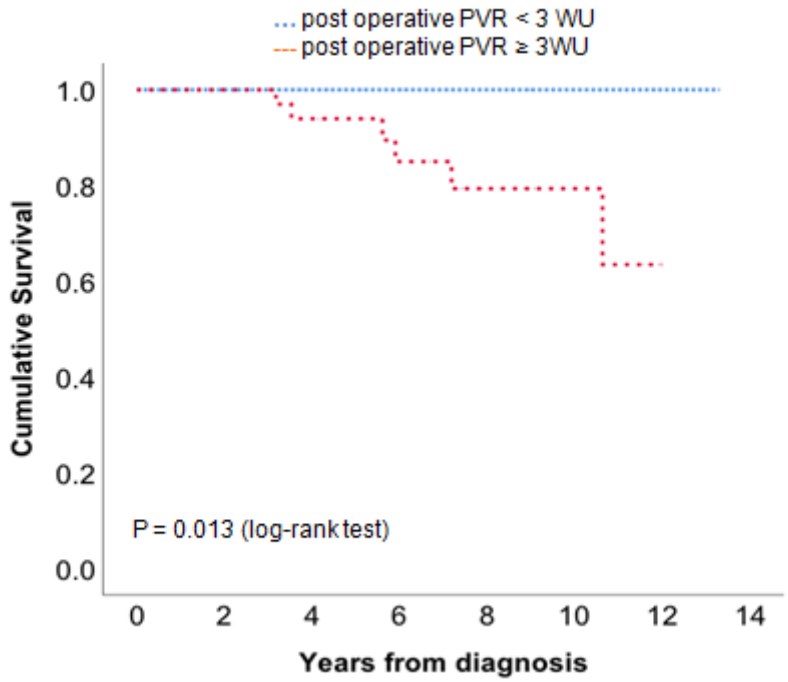
Definition of abbreviations; CTEPH = chronic thromboembolic pulmonary hypertension;

Figure 10: Kaplan-Meier estimates of survival from date of diagnosis in CTEPH patients, stratified whether they developed persistent PH post PEA surgery, log-rank test, p =0.288



Definition of abbreviations; PH = pulmonary hypertension; PEA = pulmonary endarterectomy;

Figure 11: Kaplan-Meier estimates of survival from date of diagnosis in patients with CTEPH based on their post-operative pulmonary vascular resistance on right heart catheterization, log-rank test, p =0.013



Definition of abbreviations; PVR = pulmonary vascular resitance; WU = Wood Units;

Figure 12: Kaplan-Meier estimates of survival from date of diagnosis in operated patients, stratified by whether they received bridging therapy to PEA, log-rank test, p =0.447

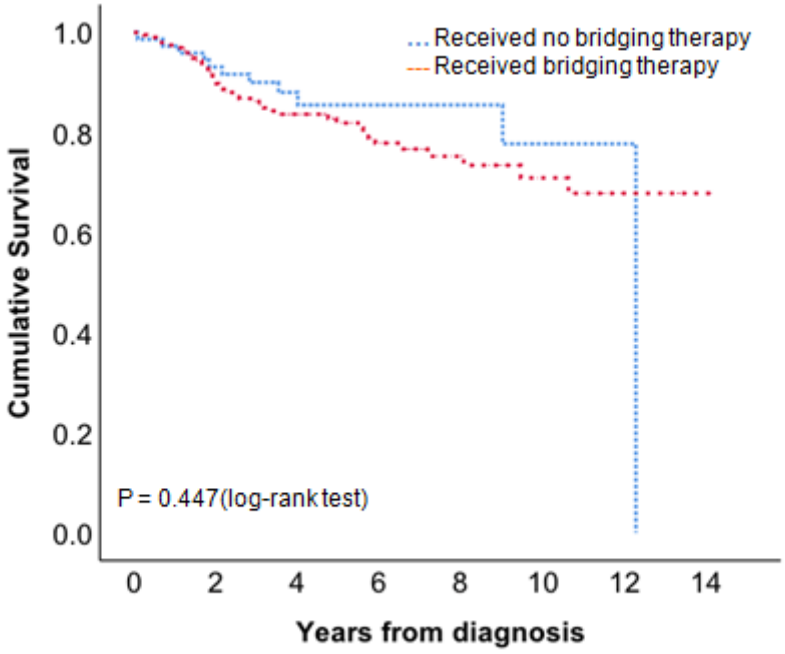
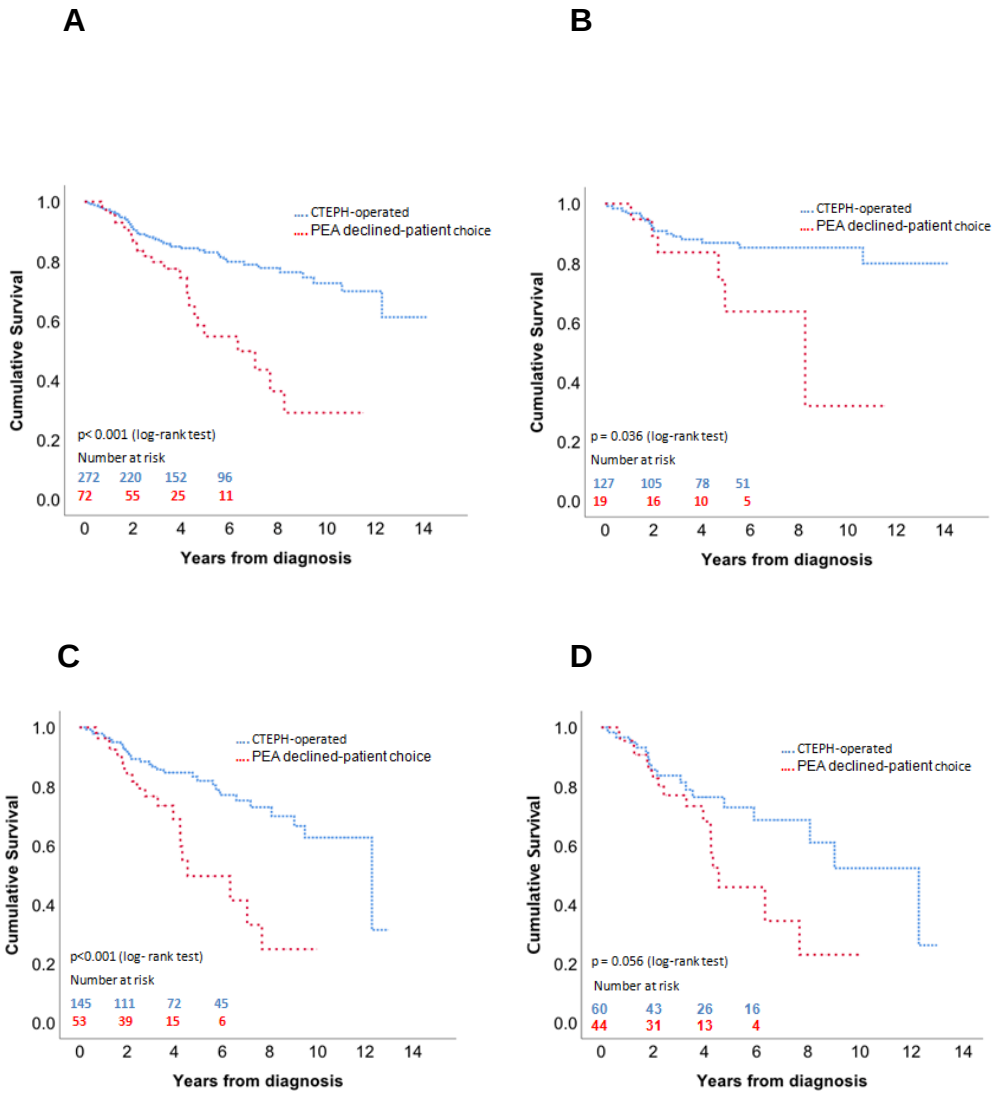


Figure 13: Kaplan-Meier estimates of survival from date of diagnosis comparing outcomes in patients with technically operable CTEPH who were offered surgery and underwent PEA versus patients who declined surgery (patient choice). A: all patients B: patients < 60 yrs, C: patients ≥ 60 years, D: patients ≥70 years



Definition of abbreviations; CTEPH = chronic thromboembolic pulmonary hypertension; PEA = pulmonary endarterectomy;

Figure 14: Kaplan-Meier estimates of survival from date of diagnosis comparing outcomes in patients with technically operable CTEPH who declined surgery (patient choice) were considered unfit for surgery or in whom comorbidities contributed to symptoms in addition to clot burden

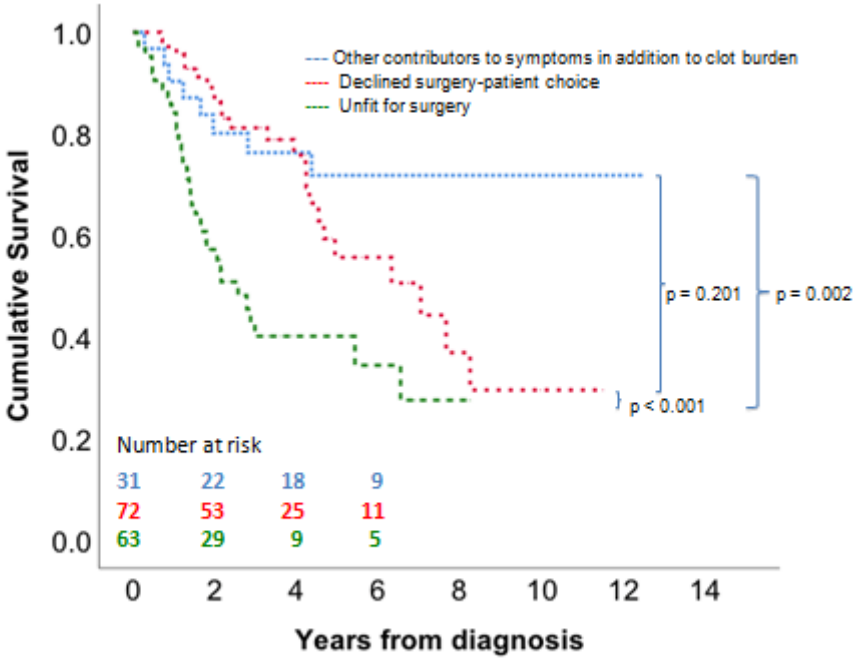


Figure 15: Kaplan-Meier estimates of survival from date of diagnosis comparing outcomes in patients with CTEPH who have undergone PEA and other contributors to symptoms in addition to clot burden, log-rank test, p = 0.281

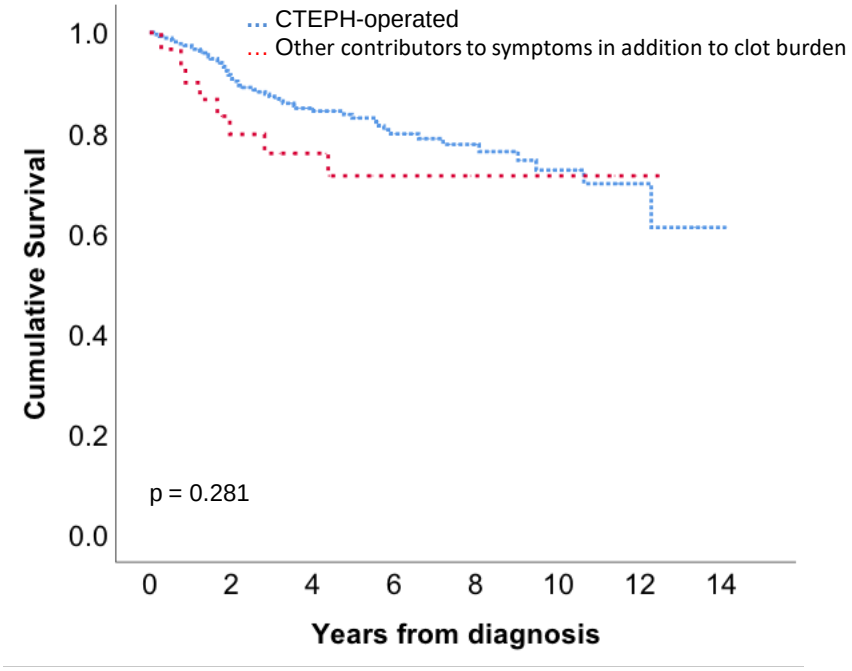


Figure 16: Kaplan-Meier estimates of survival from date of diagnosis in patients with CTEPH who underwent PEA based on their waiting time from diagnosis to surgery, log-rank test, p=0.688

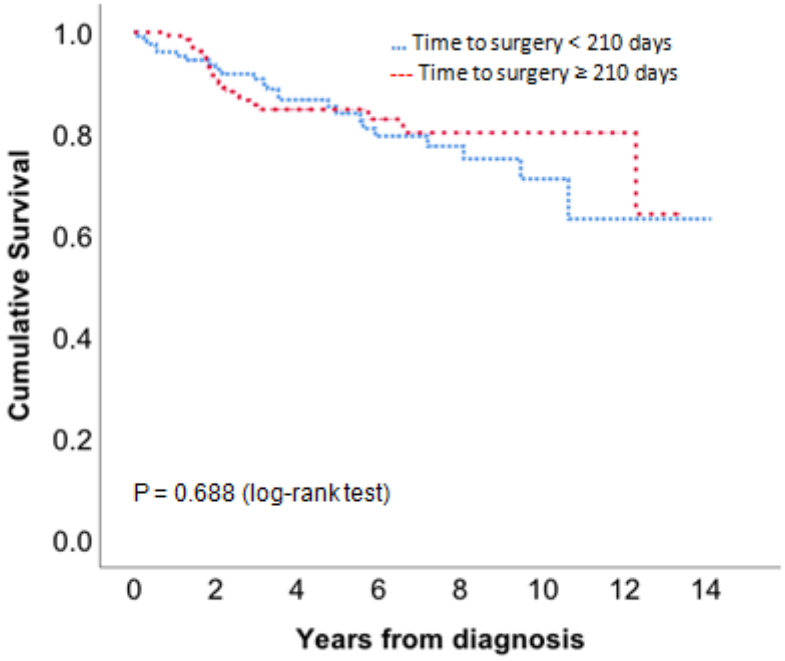
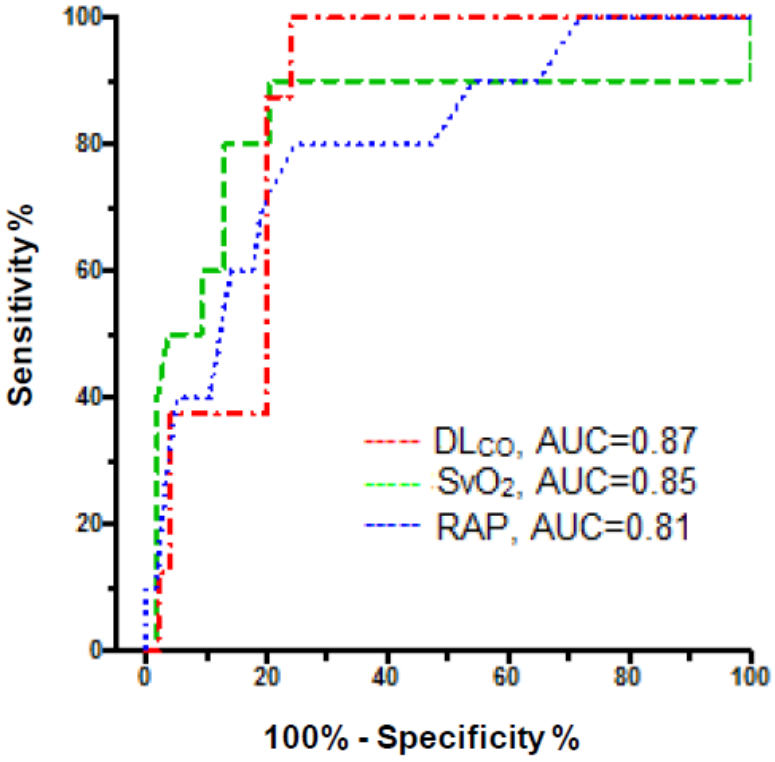
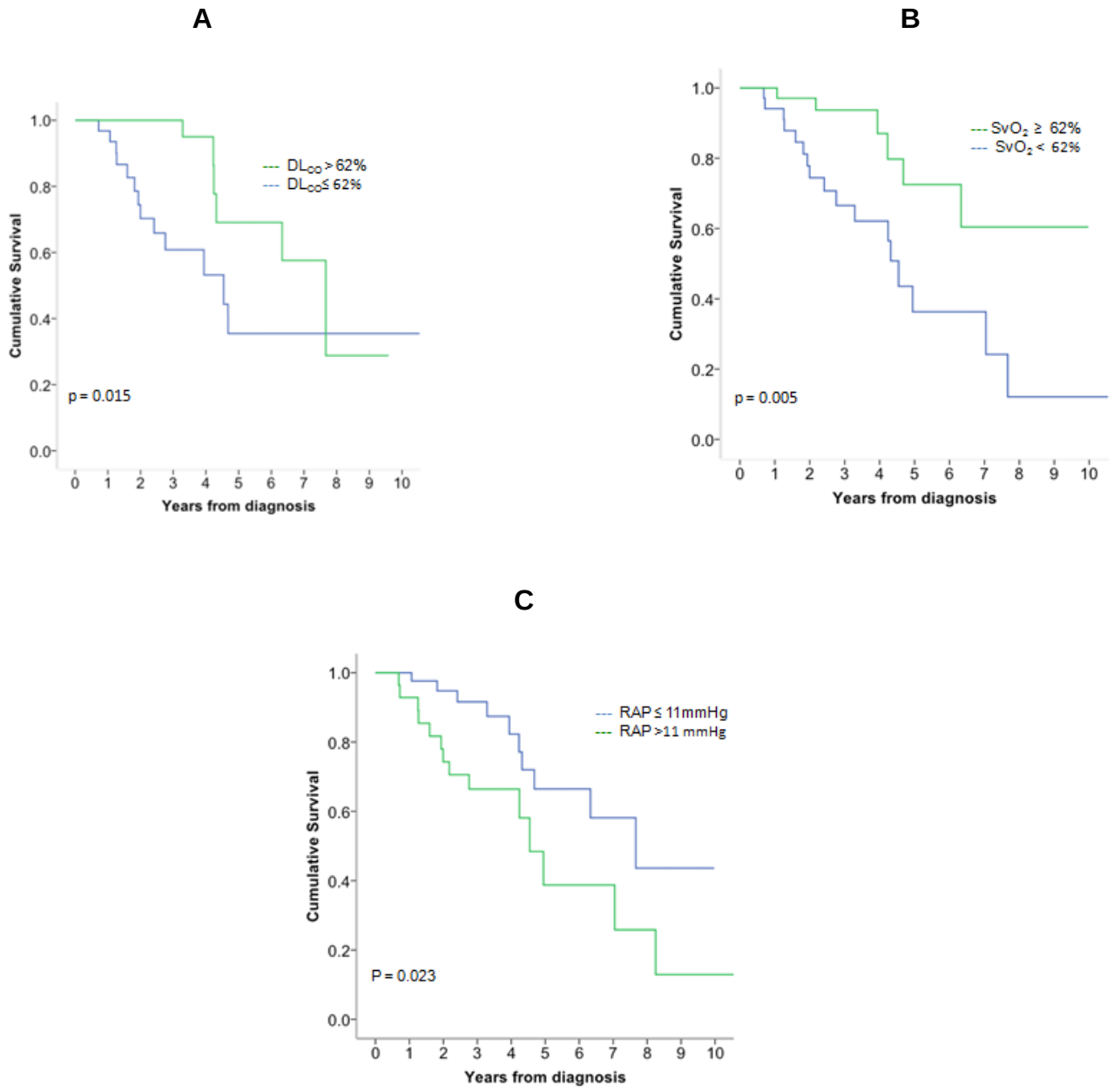


Figure 17: Accuracy of prognostic variables at three years in patients with technically operable disease who declined surgery: diffusing capacity of lung for carbon monoxide right atrial pressure and mixed venous oxygen saturation



Definition of abbreviations; D_{LCO} = diffusion capacity of carbon monoxide; SvO_2 = mixed venous oxygen saturations; RAP = right atrial pressure;

Figure 18: Kaplan-Meier estimates of survival from date of diagnosis in patients with technically operable CTEPH who declined surgery due to patient choice based on their (A) baseline gas transfer, (B) mixed venous oxygen saturations and (C) right atrial pressure



Definition of abbreviations; D_{LCO} = diffusion capacity of carbon monoxide; SvO_2 = mixed venous oxygen saturation; RAP = right atrial pressure;

Chapter 4: Successful outcomes in chronic thromboembolic pulmonary hypertension using a non-invasive imaging approach

Abstract

Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is potentially curable by pulmonary endarterectomy. Therefore, identification of patients suitable for surgery is of utmost importance in the treatment of the disease. Current guidelines recommend conventional pulmonary angiography as the final step in the diagnostic pathway. The aim of this study was to identify whether a non-invasive imaging approach in conjunction with right heart catheterisation could be used to aid treatment decisions in CTEPH with comparable outcomes to the published literature using conventional pulmonary angiography techniques.

Methods

Imaging data was analysed for CTEPH patients identified from the ASPIRE Registry between 2001 and 2014.

Results

A total of 507 patients were identified. The mean age was 63±15 years, with 49% female, 89% WHO functional class III/IV, 72% having a previous history of venous thromboembolism, mean pulmonary artery pressure 46±11mmHg and pulmonary vascular resistance 7.6±4.2 WU. Of the patients, 94% underwent multimodality imaging, 96% CT-pulmonary-angiography, 84% perfusion-MR-angiography, 78% ventilation-perfusion or perfusion-only-lung-imaging, and 2% conventional pulmonary angiography. 82% (n=418) of patients identified with CTEPH had technically operable disease. Of this 61% (n=256) of the patients underwent PEA surgery with a perioperative mortality of 3% and five-year survival of 85%.

Conclusion

By using a non-invasive multimodality imaging approach in CTEPH a proportion of patients with technically operable disease can be identified as compared to approaches based on conventional pulmonary angiography. In addition, selection of patients for surgery using a non-invasive imaging approach was associated with a low peri-operative mortality. These results highlight the value of a non-invasive multi-modality imaging approach to assess patients with CTEPH for consideration of pulmonary endarterectomy.

Introduction

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a form of pulmonary hypertension which is potentially curable by pulmonary endarterectomy. In majority of cases it follows an acute episode of pulmonary embolism but it can also present as an unexplained pulmonary hypertension with no previous history of venous thromboembolism (Pepke-Zaba et al., 2011). Characteristic imaging features of CTEPH include the presence of complete or partial vessel obstruction, luminal thrombus, webs, stenosis, post-stenotic dilatation and mosaic perfusion (Lang et al., 2010).

Traditionally, the assessment of patients with suspected CTEPH was based on initial ventilation-perfusion lung scanning with subsequent conventional pulmonary angiography and right heart catheterisation. Many of the defects demonstrated on conventional pulmonary angiography can be demonstrated on CT-pulmonary angiography (CTPA) (Ley et al., 2012). Over recent years there has been increased use of CTPA in the diagnosis of CTEPH, however conventional pulmonary angiography remains a common modality. A study done by Pepke-Zaba et al. reported that at least 63% of patients enrolled in a large international CTEPH registry had undergone conventional pulmonary angiography (Pepke-Zaba et al., 2011). MR imaging techniques have also been shown to be effective at imaging the pulmonary arterial tree. 3D-MR perfusion imaging has been demonstrated to be as sensitive as standard isotope perfusion imaging (Rajaram et al., 2013, Rajaram et al., 2012). Although current guidelines recommend CTPA following initial ventilation-perfusion imaging, conventional pulmonary angiography is recommended as the final step in the diagnostic pathway in the work up of patients with CTEPH (Galie et al., 2015). The aim of this study was to assess the outcome of patients identified with CTEPH using a first-line non-invasive multimodality imaging approach. Specifically, I wished to compare the percentages of patients with CTEPH who were identified as having surgically accessible disease and their peri-operative outcomes with contemporary

registry data including the International CTEPH Registry, to establish whether such a non-invasive imaging approach could be advocated for patients with CTEPH.

Methods

Data from the ASPIRE registry for consecutive treatment-naïve patients diagnosed with CTEPH between 2001 and 2014 at the Sheffield Pulmonary Vascular Disease Unit was reviewed. Patients with suspected CTEPH underwent first line multimodality imaging with ventilation perfusion or perfusion lung imaging and/or 3D MR and MR angiography and/or CTPA. Conventional pulmonary angiography (digital subtraction angiography) was only performed if diagnostic quality imaging was not available from 2 imaging modalities. The rest of the methods including statistical analysis have been previously described in Chapter 2.

Results

A total of 507 patients with CTEPH were identified (figure 19): mean age 63±15 years, 49% female, 89% WHO functional class III/IV with 72% having a previous history of venous thromboembolism. At right heart catheterisation, mean right atrial pressure was 11±5mmHg, mean pulmonary artery pressure 46±11mmHg, cardiac index 2.6±0.7 $L.min.m^{-2}$, pulmonary vascular resistance 7.6±4.2 WU and mixed venous oxygen saturation 61±8%. Patients undergoing surgery were younger, more likely to be male and had fewer comorbidities (table 19).

The imaging investigations that patients underwent are shown in table 20. CTPA was the most common investigation performed in 488 (96%) of patients followed by 3D MR perfusion/MR angiography 424 (84%), ventilation and perfusion/perfusion-only imaging 396 (78%). Conventional pulmonary angiography was performed in only 9 (2%) patients. Multimodality imaging was performed in 98% of patients undergoing pulmonary endarterectomy and 94% of patients not undergoing surgery. 82% of the patients identified in this study were diagnosed with technically operable disease based on the non-invasive multimodality imaging approach.

At census end date 256 patients had undergone pulmonary endarterectomy and 251 had not undergone surgery due to disease distribution, comorbidities or patient choice. Of those undergoing pulmonary endarterectomy the perioperative mortality was 3% with survival of 90% at 3 years and 85% at 5 years (figure 20). Survival in the CTEPH-not-operated group at three and five years was 70% and 55% respectively (figure 20).

Discussion

To my knowledge, this is the largest study to examine the use of a first-line non-invasive multimodality imaging approach alongside right heart catheterisation in CTEPH diagnosis and treatment assessment. This study demonstrates that this approach can accurately identify patients with technically operable disease with a low perioperative mortality and excellent long-term survival following surgery, comparable to patients undergoing conventional pulmonary angiography as reported in contemporary published literature.

82% of the patients in this study were deemed to have technically operable disease, which was similar to the data from the International CTEPH registry (where 80% of the patients were deemed to have technically operable disease) suggesting that similar proportions of patients can be identified as technically operable CTEPH by using a non-invasive multimodality imaging approach as compared to conventional pulmonary angiography (Pepke-Zaba et al., 2011, Delcroix et al., 2016).

Pulmonary endarterectomy is the treatment of choice in patients with CTEPH (Galie et al., 2015). It offers the best prospect of improved quality and quantity of life and identification of such patients is therefore paramount. I observed excellent long-term outcomes (3-year survival 90%) and low perioperative mortality (3%). These findings are comparable with multiple previous multicentre registries including the International CTEPH Registry (Delcroix et al., 2016), the Spanish Registry (Escribano-Subias et al., 2016) and the UK Pulmonary Hypertension Registry (Condliffe et al., 2008). Specifically, the international CTEPH registry,

which is the largest such registry of its kind reported a peri-operative mortality of 4.7% and a 3-year survival from diagnosis of 89%, with at least 63% of patients undergoing conventional pulmonary angiography (Pepke-Zaba et al., 2011, Delcroix et al., 2016). Demographic and haemodynamic characteristics and rates of previous venous thromboembolic disease were also comparable to the international CTEPH registry (Pepke-Zaba et al., 2011), suggesting that similar populations can be identified using low rates of conventional angiography. Although conventional pulmonary angiography may be required in the small proportion of patients who are candidates for balloon pulmonary angioplasty, a first-line non-invasive approach to identify and classify CTEPH can significantly reduce the need for an invasive procedure with its associated risks. The recently published Fleischner statement on pulmonary hypertension has highlighted the value of a multi-modality imaging approach in the assessment of CTEPH and the value of alternative techniques to conventional pulmonary angiography (Remy-Jardin et al., 2021).

Limitations

This is a single centre retrospective study assessing outcomes from a non-invasive multimodality imaging strategy in patients with CTEPH and therefore would benefit from external validation. Nonetheless, the outcomes chosen (identification of surgical disease and peri-operative mortality) and the consecutive nature of enrolment of patients with CTEPH provides a basis for further study of such a non-invasive approach. Recent expert opinion (Remy-Jardin et al., 2021) and statements from the European Respiratory Society (Delcroix et al., 2021) now also endorse such an approach as an alternative to conventional pulmonary angiography.

Conclusion

In summary, this study demonstrates that a multi-modality non-invasive imaging approach can be used to identify patients with technically operable disease with similar outcomes following surgery as compared to patients undergoing conventional pulmonary angiography. This study therefore provides an alternative to strategies utilising conventional pulmonary angiography in the management of CTEPH.

Table 19: Baseline characteristics of patients with CTEPH (operated vs not operated groups)

	CTEPH (whole-cohort) (n = 507)	**CTEPH-operated (n = 256)**	**CTEPH-not - operated (n = 251)**	**p-value**
Age (years)	63 (15)	58 (15)	68 (14)	<0.001
Gender (%, Female)	49%	44%	54%	0.019
BMI ($kg.m^{-2}$)	29 (7)	30 (7)	29 (7)	0.471
WHO FC (I/II vs III/IV) %	11/89	14/87	9/91	0.138
ISWD (m)	195 (181)	235 (188)	154 (163)	<0.001
RAP (mmHg)	11 (5)	11 (6)	11 (5)	0.828
mPAP (mmHg)	46 (11)	47 (11)	45 (11)	0.139
CI ($L.min.m^{-2}$)	2.6 (0.7)	2.6 (0.7)	2.6 (0.8)	0.275
PAWP (mmHg)	12 (5)	12 (4)	12 (5)	0.478
PVR (WU)	7.6 (4.2)	7.7 (4.1)	7.5 (4.3)	0.668
SvO_2 (%)	61 (8)	61 (8)	62 (9)	0.574
FEV_1 (% predicted)	80 (36)	84 (45)	77 (23)	0.043
D_{LCO} (% predicted)	61 (17)	65 (15)	57 (18)	<0.001
Previous acute VTE (%)	72	75	70	0.184
Cancer (%)	11	6	16	0.001
CAD (%)	11	11	12	0.826
COPD (%)	20	14	27	<0.001
LV dysfunction (%)	5	2	7	0.017
CKD (%)	7	3	10	0.001
Obesity (%)	36	39	32	0.091

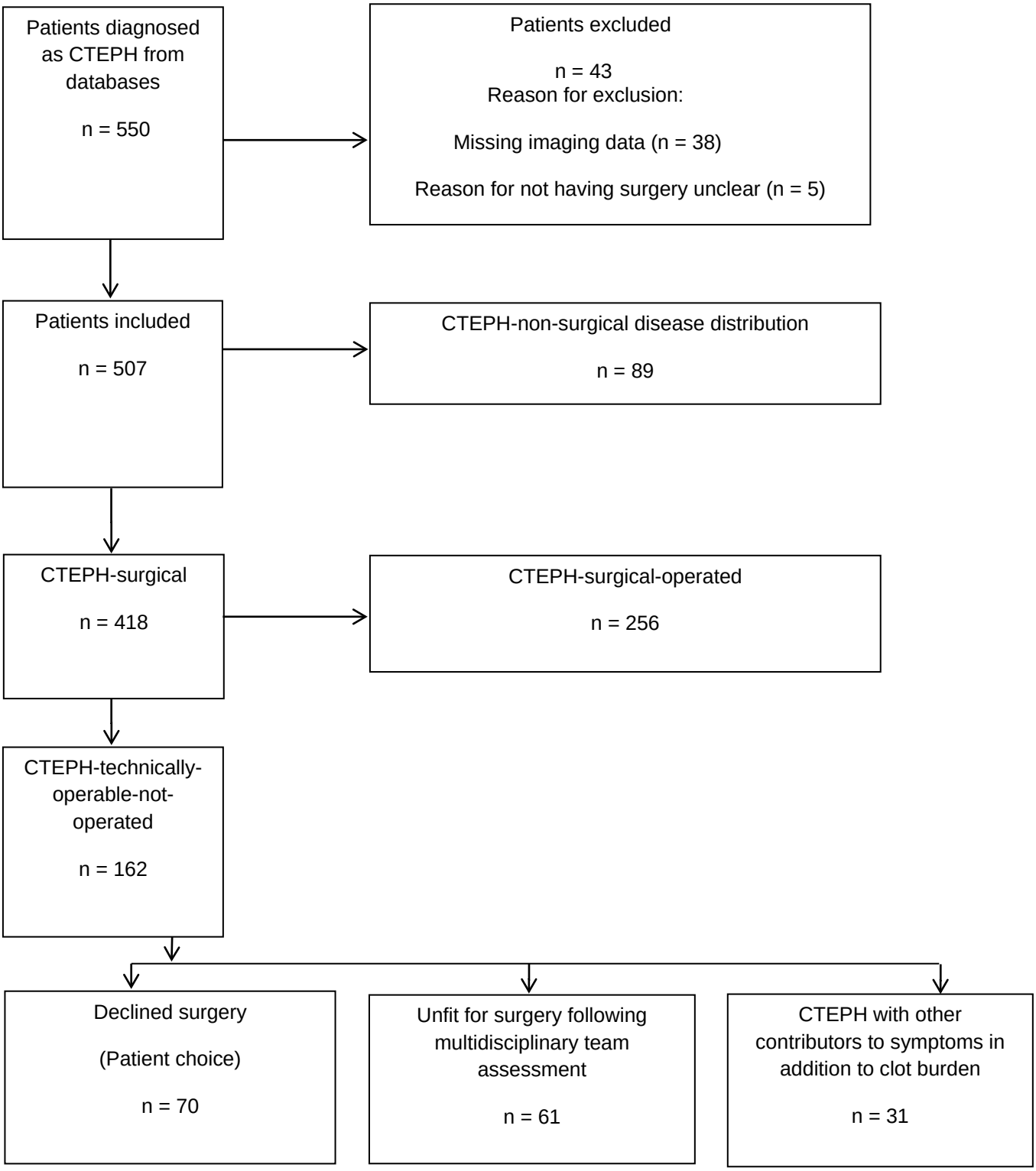
Definition of abbreviations: n = number of patients; BMI = body mass index; WHO FC = World Health Organization functional class; ISWD = incremental shuttle walk distance; RAP = right atrial pressure; mPAP = mean pulmonary arterial pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; FEV_1 = forced expiratory volume in one second; D_{LCO} = diffusion capacity of lung for carbon monoxide; VTE = venous thromboembolism; PE = pulmonary embolism; CAD = coronary artery disease; LV = left ventricle; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PH = pulmonary hypertension;
Values are mean (standard deviation) or percentage unless otherwise indicated. Mean.
P-value was calculated by using t- test for continuous variables and Chi-squared test for categorical variables.

Table 20: Imaging modalities used to establish a diagnosis of CTEPH

Imaging modality	CTEPH whole cohort (n = 507)	CTEPH operated (n = 256)	CTEPH not operated (n = 251)
CTPA, Perfusion MRA, Scintigram	334 (68%)	185(72%)	159 (63%)
CTPA, Perfusion MRA	74 (15%)	34 (13%)	40 (16%)
CTPA, Scintigram	53 (10%)	20 (8%)	33 (13%)
CTPA only	18 (4%)	4 (2%)	14 (6%)
Perfusion MRA, Scintigram	8 (2%)	5 (2%)	3 (1%)
CTPA, Perfusion MRA, DSA	8 (2%)	7 (3%)	2 (1%)
CTPA, Scintigram, DSA	1(0.2%)	1 (0.5%)	0 (0%)
DSA only	0 (0%)	0 (0%)	0 (0%)
Scintigram only	0 (0%)	0 (0%)	0 (0%)

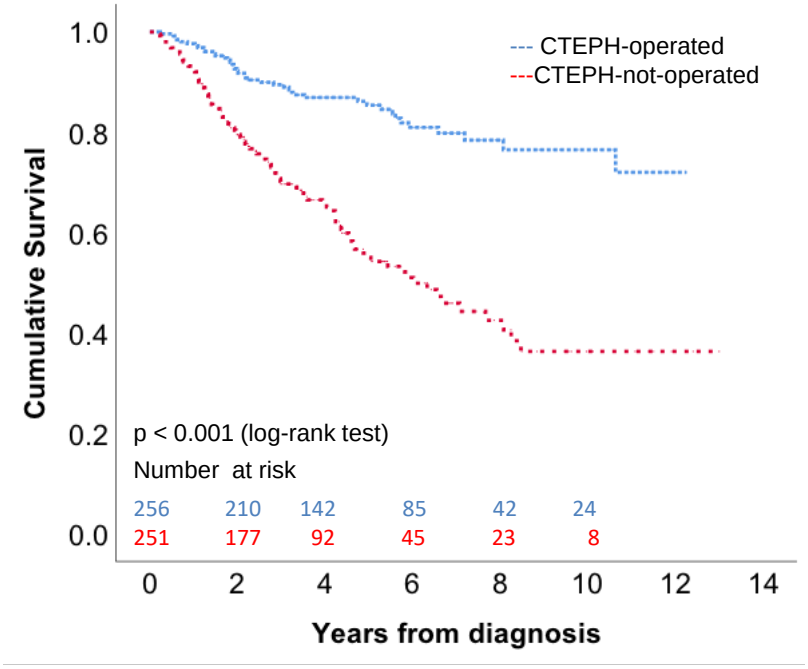
Definition of abbreviations: n = number of patients; CTPA = computed tomographic pulmonary angiogram; Perfusion MRA = 3D magnetic resonance perfusion map and magnetic resonance angiogram; DSA = digital subtraction angiography (conventional pulmonary angiogram); Values are expressed as mean (standard deviation) or percentage.

Figure 19: Patient cohort



Definition of abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension; n = number of patients;

Figure 20: Kaplan-Meier estimates of survival from date of diagnosis comparing outcomes in CTEPH operated and not operated patients



Definition of abbreviation; CTEPH= chronic thromboembolic pulmonary hypertension;

Chapter 5: Conclusion and outlook

In this thesis I have described the baseline characteristics, the long-term survival rates, and identified prognostic indicators in patients with newly diagnosed CTEPH with a focus on patients with technically operable disease who have not undergone surgery and have explored associations. Data from my thesis has shown that CTEPH includes a wide spectrum of disease which impacts on long-term survival. I have confirmed that patients with CTEPH who have technically operable disease and are judged to be candidates for surgery have an excellent long-term survival following PEA. Importantly, I have shown for the first time that in a large cohort of patients with CTEPH the long-term survival of patients undergoing surgery is superior to patients who were offered but declined surgery. I have also identified several factors that may aid clinical decision making and help stratify patients who are potential candidates for surgery into higher or lower risk of mortality groups.

The data in this thesis has shown an increase in the number of patients diagnosed with CTEPH annually at the study unit over the last decade, with diagnostic rates now in excess of 5/million/year. It is not entirely clear as to the cause of the increased diagnostic rates, however, it is likely that this reflects an increased awareness amongst healthcare professionals of CTEPH coupled with the more recent availability of effective therapies. It will of course be interesting to assess in the coming years whether more aggressive approaches to long-term anticoagulation that reflect improved stratification of those at highest and lowest risk of recurrent thromboembolic disease may reduce the burden of CTEPH. In the interim, approaches to raise awareness and to develop specific clinics for the follow-up of patients following an acute pulmonary embolism may aid improved identification of patients with CTEPH (De-Fonseka D, 2014). Deployment of such clinics in Sheffield has achieved diagnostic rates in excess of 10/million/ year, more than double diagnostic rates in areas where there is no dedicated follow-up of patients following pulmonary embolism.

My main finding in this study is the superior survival of patients with CTEPH who underwent surgery compared to patients who were eligible for surgery but turned it down. Patients who

declined surgery were more likely to be female, 10 years older and had more co-morbidities compared to patients who underwent surgery which does put them at a higher risk of post-surgical mortality. Nonetheless, following multivariate analyses when important prognostic markers were taken into account the decision to decline surgery remained an important independent predictor of a worse outcome. The proportion of patients who declined surgery was much higher in my study compared to other registries including the international CTEPH registry but in line with the data from the National PEA centre at the Royal Papworth Hospital at Cambridge where data from consecutive patients with CTEPH was also collected. This can be explained by one of the limitations of the International CTEPH Registry which was the selected nature of patient enrolment. This had likely enriched this population for patients undergoing surgery. Very importantly, given that the survival of patients who undergo surgery is vastly superior to those who were offered surgery but declined, this study highlights the importance of how we provide information and counsel patients. One outcome from this study is a recognition of the need to explore factors underpinning decision making and whether there are additional tools that may aid this decision-making process. Extra counselling of patients who decline surgery (whilst respecting the patient's wishes) may give them more time and opportunity to improve rapport and trust with the treating healthcare professionals. This might also help them accept the difficult realities of life to and come to a truly fully informed decision.

In this thesis I have also identified prognostic indicators (D_{LCO} of 62%, RAP of 11mmg Hg and SvO_2 of 62%) with excellent negative predictive values in patients who have declined surgery. This may help in counselling patients and aid in clinical decision making. Being able to stratify patients into poor short and medium-term outcome groups based on these prognostic indicators may be helpful in counselling strategies. In patients who are identified at low-risk of short and medium-term mortality, particularly older patients who decline surgery, this may provide reassurance that not having the surgical intervention may not impact them prognostically, although it would be expected to benefit them symptomatically. Whereas in

patients who have adverse prognostic indicators they may be more inclined to consider a surgical intervention.

One of the unexpected findings of this study was that women were more likely to decline surgery than men. Interestingly, there is data in the literature including from the gambling industry, on the impact of sex on risk taking. How patients are counselled and whether the sex or gender of the patient influences this is not explored by this study. However, as a follow-on from this thesis a study can be proposed that explores in patients with CTEPH the factors that influence their decision-making around treatment. This proposal includes conducting a qualitative and quantitative survey of patients and their families who accepted or declined surgery. In addition, there is also a plan to interview medical staff including pulmonary vascular physicians, PEA surgeons and specialist nurses. Discussions are currently on-going with stakeholders including with the UK patient charity (PHA-UK) and the University of Manchester to take this work forward. Finally, with respect to surgery, this study provides further data supporting the prognostic value of PEA for CTEPH. In the multivariate analysis I found that having PEA was one of the strongest predictors of survival in patients with CTEPH. A randomized control trial (RCT) randomising patients with CTEPH and operable disease to surgery or medical therapy would provide the highest level of evidence but given the overwhelming data conducting such a study would be considered unethical.

In this thesis I was also able to demonstrate in a large cohort of patients with CTEPH that a non-invasive multimodality imaging approach can be used alongside right heart catheterisation to diagnose patients with technically operable disease with outcomes and the proportions of patients undergoing surgery similar to other reports in contemporaneous registries. Thus, it offers an alternative to the guidelines from 2015 regarding imaging approaches in the diagnosis of the disease.

The main weakness in this study was the absence of a comparator group (patients undergoing conventional pulmonary angiogram) and lack of access to raw data from other registries (including the International CTEPH registry). When they are widely available in clinical practice, newer imaging techniques such as cone beam CT and dual energy CT could potentially replace conventional pulmonary angiogram (CPA) in the future to study the distal pulmonary vasculature. Although a non-invasive approach may be helpful when deciding on whether patients are candidates for surgery the advent of balloon pulmonary angioplasty means that conventional pulmonary angiography will remain an important part of the assessment of selected patients with CTEPH who are not considered surgical candidates and cases where non-invasive imaging is non-diagnostic. Importantly, the multimodality imaging approach highlighted in this thesis has been recognised as an important part of the assessment of patients with CTEPH by a recently published report form the Fleischner Society (Remy-Jardin et al., 2021).

Over the last 20 years the treatment of CTEPH has evolved and there has been a recent move to combine treatment modalities. There is also an increasing interest in lowering the risk of mortality by reducing pulmonary vascular resistance either prior to surgery or balloon pulmonary angioplasty. In this thesis I found that majority of the patients were treated with sildenafil as a bridge to surgery and pre-treatment was not associated with a worse outcome as has been highlighted in the International CTEPH Registry. It is possible that the higher mortality in the International CTEPH Registry in patients treated with drug therapy may have been related to delaying or reducing access to surgery. Survival following surgery was similar in this study and the international CTEPH registry. I also showed that time to surgery was not a prognostic indicator for the population as a whole. Several RCTs are currently underway which are looking at the role of riociguat as a single agent as a bridge to surgery. Interestingly, despite the off-label use of sildenafil in CTEPH and small studies previously performed in single centres there is no multicentre RCT data for sildenafil as a treatment for CTEPH.

One of the challenges during my thesis was related to collection of data. I encountered significant delays due to my ambitions to build a user-friendly database that could be used to prospectively enter data of patients after the completion of my study. It took a considerable amount of my research time to create the data collection software. In addition, I faced multiple challenges including information governance issues. Despite investing significant amounts of time and efforts seeking a local in-house solution none was forthcoming. On reflection it may have been a missed opportunity not to have contacted the International CTEPH registry to have asked for permission to use their web-based data collection software.

Furthermore, one of my ambitions had been to consider whether the assessment of patients with CTEPH could be done entirely non-invasively and without the need for right heart catheterization. However, right heart catheterization remains the gold standard for the assessment of pressure and PVR, the latter a well validated tool aiding the selection of patients for surgery. Whether, such estimates of PVR and pressure could be made non-invasively requires further study although the database and imaging warehouse that I have helped establish may allow a subsequent colleague to explore this potential area of research, particularly in exploring the use of non-invasive imaging to assess haemodynamic severity and to assess whether incorporating AI techniques can more accurately predict peri-operative mortality.

Another one of the big changes that occurred during the conduction of my thesis has been the development of BPA as a treatment of CTEPH and the licensing of riociguat as a treatment for non-surgical CTEPH in subsequent years. In this thesis no patients underwent BPA or received treatment with riociguat, as these treatment options were not available during that time. These are now standard treatment options for patients with non-operable CTEPH in the UK. RCT's comparing riociguat versus BPA in patients with distal disease are underway as are clinical trials of multimodality approaches to the treatment of CTEPH. Nonetheless I do feel that my contribution to this rapidly evolving field has been significant by providing important

information that can guide patients with respect to decision making regarding PEA. One of the weaknesses of this study was its single centre nature. However, a recent publication from the large multicentre COMPERA Registry has confirmed my findings with respect to the negative impact of declining surgery on outcome in CTEPH.

In conclusion, this thesis highlights that more work needs to be undertaken to understand the reasons why patients with CTEPH who are offered surgery decline to undergo the procedure. Which factors in particular motivate patients, whether there are differences in how physicians and surgeons counsel patients and what specific counselling approaches may benefit particular groups of patients are the questions that need exploring. By highlighting these areas for further work, I hope my contribution to the field will improve outcomes for patients with CTEPH.

Bibliography

2018. Clinical Commissioning Policy: Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (all ages), NHS England.

BONDERMAN, D., SKORO-SAJER, N., JAKOWITSCH, J., ADLBRECHT, C., DUNKLER, D., TAGHAVI, S., KLEPETKO, W., KNEUSSL, M. & LANG, I. M. 2007. Predictors of outcome in chronic thromboembolic pulmonary hypertension. *Circulation,* 115**,** 2153-8.

BUNCLARK, K., NEWNHAM, M., CHIU, Y. D., RUGGIERO, A., VILLAR, S. S., CANNON, J. E., COGHLAN, G., CORRIS, P. A., HOWARD, L., JENKINS, D., JOHNSON, M., KIELY, D. G., NG, C., SCREATON, N., SHEARES, K., TABOADA, D., TSUI, S., WORT, S. J., PEPKE-ZABA, J. & TOSHNER, M. 2020. A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension. *J Thromb Haemost,* 18**,** 114-122.

BUNCLARK, K. A., N. ALMEIDA, A. CANNON, J. CLARE, S. DOUGHTY, N. DUNNING, J. NG, C. NEWNHAM, M. PONNABERANAM, A. RUGGIERO, A. SCREATON, N. SHEARES, K. SPEED, N. TABOADA, D. TOSHNER, M. TSUI, S. JENKINS, D. PEPKE-ZABA, J. 2017. Patient pathway mapping of uk referrals to the national pulmonary endarterectomy mdt (june 2015 – may 2016). *Thorax,* 72**,** A33-A34.

CANNON JE, P.-Z. J. 2013. Is Distal Chronic Thromboembolic Pulmonary Hypertension Treatable with PAH Targeted Drugs? *Semin Respir Crit Care Med* 34**,** 620-626.

CANNON, J. E., SU, L., KIELY, D. G., PAGE, K., TOSHNER, M., SWIETLIK, E., TREACY, C., PONNABERANAM, A., CONDLIFFE, R., SHEARES, K., TABOADA, D., DUNNING, J., TSUI, S., NG, C., GOPALAN, D., SCREATON, N., ELLIOT, C., GIBBS, S., HOWARD, L., CORRIS, P., LORDAN, J., JOHNSON, M., PEACOCK, A., MACKENZIE-ROSS, R., SCHREIBER, B., COGHLAN, G., DIMOPOULOS, K., WORT, S. J., GAINE, S., MOLEDINA, S., JENKINS, D. P. & PEPKE-ZABA, J. 2016. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. *Circulation,* 133**,** 1761-71.

CONDLIFFE, R., KIELY, D. G., GIBBS, J. S., CORRIS, P. A., PEACOCK, A. J., JENKINS, D. P., GOLDSMITH, K., COGHLAN, J. G. & PEPKE-ZABA, J. 2009. Prognostic and aetiological factors in chronic thromboembolic pulmonary hypertension. *Eur Respir J,* 33**,** 332-8.

CONDLIFFE, R., KIELY, D. G., GIBBS, J. S., CORRIS, P. A., PEACOCK, A. J., JENKINS, D. P., HODGKINS, D., GOLDSMITH, K., HUGHES, R. J., SHEARES, K., TSUI, S. S., ARMSTRONG, I. J., TORPY, C., CRACKETT, R., CARLIN, C. M., DAS, C., COGHLAN, J. G. & PEPKE-ZABA, J. 2008. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med,* 177**,** 1122-7.

COQUOZ, N., WEILENMANN, D., STOLZ, D., POPOV, V., AZZOLA, A., FELLRATH, J. M., STRICKER, H., PAGNAMENTA, A., OTT, S., ULRICH, S., GYORIK, S., PASQUIER, J. & AUBERT, J. D. 2018. Multicentre observational screening survey for the detection of CTEPH following pulmonary embolism. *Eur Respir J,* 51.

CORSICO, A. G., D'ARMINI, A. M., CERVERI, I., KLERSY, C., ANSALDO, E., NINIANO, R., GATTO, E., MONTEROSSO, C., MORSOLINI, M., NICOLARDI, S., TRAMONTIN, C., POZZI, E. & VIGANO, M. 2008. Long-term outcome after pulmonary endarterectomy. *Am J Respir Crit Care Med,* 178**,** 419-24.

D'ARMINI, A. M., MORSOLINI, M., MATTIUCCI, G., GRAZIOLI, V., PIN, M., VALENTINI, A., SILVAGGIO, G., KLERSY, C. & DORE, R. 2014. Pulmonary endarterectomy for distal chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg,* 148**,** 1005-11; 1012 e1-2; discussion 1011-2.

DARTEVELLE, P., FADEL, E., MUSSOT, S., CHAPELIER, A., HERVE, P., DE PERROT, M., CERRINA, J., LADURIE, F. L., LEHOUEROU, D., HUMBERT, M., SITBON, O. & SIMONNEAU, G. 2004. Chronic thromboembolic pulmonary hypertension. *Eur Respir J,* 23**,** 637-48.

DE-FONSEKA D, C. R., ELLIOT CA, HURDMAN J, MACLEAN R, KIELY DG 2014. Incidence and severity of Chronic Thromboembolic Pulmonary Hypertension following the introduction of one stop clinic for Acute Pulmonary Embolism. *Thorax,* 69**,** A63-A64.

DELCROIX, M., LANG, I., PEPKE-ZABA, J., JANSA, P., D'ARMINI, A. M., SNIJDER, R., BRESSER, P., TORBICKI, A., MELLEMKJAER, S., LEWCZUK, J., SIMKOVA, I., BARBERA, J. A., DE PERROT, M., HOEPER, M. M., GAINE, S., SPEICH, R., GOMEZ-SANCHEZ, M. A., KOVACS, G., JAIS, X., AMBROZ, D., TREACY, C., MORSOLINI, M., JENKINS, D., LINDNER, J., DARTEVELLE, P., MAYER, E. & SIMONNEAU, G. 2016. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. *Circulation,* 133**,** 859-71.

DELCROIX, M., STAEHLER, G., GALL, H., GRUNIG, E., HELD, M., HALANK, M., KLOSE, H., VONK-NOORDEGRAAF, A., ROSENKRANZ, S., PEPKE-ZABA, J., OPITZ, C. F., GIBBS, J. S. R., LANGE, T. J., TSANGARIS, I., HUSCHER, D., PITTROW, D., OLSSON, K. M. & HOEPER, M. M. 2018. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. *Eur Respir J,* 52.

DELCROIX, M., TORBICKI, A., GOPALAN, D., SITBON, O., KLOK, F. A., LANG, I., JENKINS, D., KIM, N. H., HUMBERT, M., JAIS, X., VONK NOORDEGRAAF, A., PEPKE-ZABA, J., BRENOT, P., DORFMULLER, P., FADEL, E., GHOFRANI, H. A., HOEPER, M. M., JANSA, P., MADANI, M., MATSUBARA, H., OGO, T., GRUNIG, E., D'ARMINI, A., GALIE, N., MEYER, B., CORKERY, P., MESZAROS, G., MAYER, E. & SIMONNEAU, G. 2021. ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J,* 57.

KIELY, DG. 2021. National Audit of Pulmonary Hypertension Great Britain, 2019-2020. *Great Britain, 21 January 2021. Eleventh Annual Report.*

ESCRIBANO-SUBIAS, P., DEL POZO, R., ROMAN-BROTO, A., DOMINGO MORERA, J. A., LARA-PADRON, A., ELIAS HERNANDEZ, T., MOLINA-FERRAGUT, L., BLANCO, I., CORTINA, J., BARBERA, J. A. & INVESTIGATORS, R. 2016. Management and outcomes in chronic thromboembolic pulmonary hypertension: From expert centers to a nationwide perspective. *Int J Cardiol,* 203**,** 938-44.

FEINSTEIN, J. A., GOLDHABER, S. Z., LOCK, J. E., FERNDANDES, S. M. & LANDZBERG, M. J. 2001. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. *Circulation,* 103**,** 10-3.

GALIE, N., HUMBERT, M., VACHIERY, J. L., GIBBS, S., LANG, I., TORBICKI, A., SIMONNEAU, G., PEACOCK, A., VONK NOORDEGRAAF, A., BEGHETTI, M., GHOFRANI, A., GOMEZ SANCHEZ, M. A., HANSMANN, G., KLEPETKO, W., LANCELLOTTI, P., MATUCCI, M., MCDONAGH, T., PIERARD, L. A., TRINDADE, P. T., ZOMPATORI, M. & HOEPER, M. 2015. 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 Respir J,* 46**,** 903-75.

GALL, H., HOEPER, M. M., RICHTER, M. J., CACHERIS, W., HINZMANN, B. & MAYER, E. 2017. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. *Eur Respir Rev,* 26.

GENTA, P., JATENE, F. & TERRA-FILHO, M. 2005. Quality of life before and after pulmonary thromboendarterectomy: Preliminary results. *Jornal Brasileiro de Pneumologia,* 31**,** 48-51.

GHOFRANI, H. A., D'ARMINI, A. M., GRIMMINGER, F., HOEPER, M. M., JANSA, P., KIM, N. H., MAYER, E., SIMONNEAU, G., WILKINS, M. R., FRITSCH, A., NEUSER, D., WEIMANN, G. & WANG, C. 2013. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension. *New England Journal of Medicine,* 369**,** 319-329.

GHOFRANI, H. A., SIMONNEAU, G., D'ARMINI, A. M., FEDULLO, P., HOWARD, L. S., JAIS, X., JENKINS, D. P., JING, Z. C., MADANI, M. M., MARTIN, N., MAYER, E., PAPADAKIS, K., RICHARD, D., KIM, N. H. & INVESTIGATORS, M. S. 2017. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir Med,* 5**,** 785-794.

GIBBS, J. S. R. 2017. National Audit of Pulmonary Hypertension Great Britain, 2016-17.

GIBBS, J. S. R. 2018. National Audit of Pulmonary Hypertension Great Britain, 2017-18.

GIBBS S, PEACOCK A, JOHNSON & D, K. 2011. National Audit of Pulmonary Hypertension 2011. *Thorax,* 67**,** 371-3.

GLIKLICH, R. & CAMPION, F. X. 2010. Patient registries. *MGMA Connex,* 10**,** 15-7.

HARRIS, C., JENKINS, M.,GLASER, D 2006. Gender differences in risk assessment: Why do women take fewer risks than men? . *Judgment and Decision Making,* 1**,** 48-63.

HASSOUN, P. M., MOUTHON, L., BARBERA, J. A., EDDAHIBI, S., FLORES, S. C., GRIMMINGER, F., JONES, P. L., MAITLAND, M. L., MICHELAKIS, E. D., MORRELL, N. W., NEWMAN, J. H., RABINOVITCH, M., SCHERMULY, R., STENMARK, K. R., VOELKEL, N. F., YUAN, J. X. J. & HUMBERT, M. 2009. Inflammation, Growth Factors, and Pulmonary Vascular Remodeling. *Journal of the American College of Cardiology,* 54**,** S10-S19.

HE J, FANG W, LV B, HE JG, XIONG C M, ZH, L. & X, H. Z. 2012. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. *Nuclear Medicine Communications,* 33**,** 459-463.

HOEPER, M. M., KRAMM, T., WILKENS, H., SCHULZE, C., SCHAFERS, H. J., WELTE, T. & MAYER, E. 2005. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest,* 128**,** 2363-2367.

HOEPER, M. M., MAYER, E., SIMONNEAU, G. & RUBIN, L. J. 2006. Chronic thromboembolic pulmonary hypertension. *Circulation,* 113**,** 2011-20.

HUMBERT M 2010. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. *Eur Respir Rev,* 115**,** 59-63.

HURDMAN, J., CONDLIFFE, R., ELLIOT, C. A., DAVIES, C., HILL, C., WILD, J. M., CAPENER, D., SEPHTON, P., HAMILTON, N., ARMSTRONG, I. J., BILLINGS, C., LAWRIE, A., SABROE, I., AKIL, M., O'TOOLE, L. & KIELY, D. G. 2012. ASPIRE registry: Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. *European Respiratory Journal,* 39**,** 945-955.

INAMI, T., KATAOKA, M., YANAGISAWA, R., ISHIGURO, H., SHIMURA, N., FUKUDA, K., YOSHINO, H. & SATOH, T. 2016. Long-Term Outcomes After Percutaneous Transluminal Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension. *Circulation,* 134**,** 2030-2032.

JAIS, X., D'ARMINI, A. M., JANSA, P., TORBICKI, A., DELCROIX, M., GHOFRANI, H. A., HOEPER, M. M., LANG, I. M., MAYER, E., PEPKE-ZABA, J., PERCHENET, L., MORGANTI, A., SIMONNEAU, G., RUBIN, L. J. & GRP, B. S. 2008. Bosentan for Treatment of Inoperable Chronic Thromboembolic Pulmonary Hypertension. *Journal of the American College of Cardiology,* 52**,** 2127-2134.

JAMIESON SW, T. P., FEDULLO PF, AUGER WR 2003. Pulmonary Endarterctomy: experience and lessons learned in 1500 cases. . *Ann Thorac Surg,* 76**,** 1457-1462.

JENKINS, D., MADANI, M., FADEL, E., D'ARMINI, A. M. & MAYER, E. 2017. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev,* 26.

JENKINS, D., MAYER, E., SCREATON, N. & MADANI, M. 2012. State-of-the-art chronic thromboembolic pulmonary hypertension diagnosis and management. *Eur Respir Rev,* 21**,** 32-9.

KIM, N., DELCROIX, M., JAIS, X ., MADANI, M., MATSUBARA, H., MAYER, E., OGO, T., TAPSON, V., GHOFRANI, H.,., JENKINS, D., CHANNICK ., MCLAUGHLIN, V., MCCONNELL, J., DAVID POCH ., BRAND , M., MUROS-LE ROUZIC E., SELEJ, M., AND CHIN, K., 2018a. Macitentan in chronic thromboembolic pulmonary hypertension (CTEPH): experience from the OPUS registry. *European Respiratory Journal*

KIM, N. D., M. JAIS, X . MADANI, M. MATSUBARA, H. MAYER, E. OGO, T. TAPSON, V. GHOFRANI, H. JENKINS, D. 2018b. Chronic thromboembolic pulmonary hypertension. *European Repiratory Journal***,** 1-10.

KIM, N. H., DELCROIX, M., JENKINS, D. P., CHANNICK, R., DARTEVELLE, P., JANSA, P., LANG, I., MADANI, M. M., OGINO, H., PENGO, V. & MAYER, E. 2013. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol,* 62**,** D92-9.

KONSTANTINIDES, S. V. 2014. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *European Heart Journal,* 35**,** 3145-3146.

KORSHOLM, K., ANDERSEN, A., MELLEMKJAER, S., NIELSEN, D. V., KLAABORG, K. E., ILKJAER, L. B. & NIELSEN-KUDSK, J. E. 2017. Results from more than 20 years of surgical pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension in Denmark. *Eur J Cardiothorac Surg,* 52**,** 704-709.

LANG, I. M. 2004. Chronic thromboembolic pulmonary hypertension--not so rare after all. *N Engl J Med,* 350**,** 2236-8.

LANG, I. M., DORFMULLER, P. & VONK NOORDEGRAAF, A. 2016. The Pathobiology of Chronic Thromboembolic Pulmonary Hypertension. *Ann Am Thorac Soc,* 13 Suppl 3**,** S215-21.

LANG, I. M., PLANK, C., SADUSHI-KOLICI, R., JAKOWITSCH, J., KLEPETKO, W. & MAURER, G. 2010. Imaging in Pulmonary Hypertension. *Jacc-Cardiovascular Imaging,* 3**,** 1287-1295.

LANG, I. M., SIMONNEAU, G., PEPKE-ZABA, J. W., MAYER, E., AMBROZ, D., BLANCO, I., TORBICKI, A., MELLEMKJAER, S., YAICI, A. & DELCROIX, M. 2013. Factors associated with diagnosis and operability of chronic thromboembolic pulmonary hypertension A case-control study. *Thrombosis and Haemostasis,* 110**,** 83-91.

LANGER, F., SCHRAMM, R., BAUER, M., TSCHOLL, D., KUNIHARA, T. & SCHAFERS, H. J. 2004. Cytokine response to pulmonary thromboendarterectomy. *Chest,* 126**,** 135-41.

LEWCZUK, J., PISZKO, P., JAGAS, J., PORADA, A., WOJCIAK, S., SOBKOWICZ, B. & WRABEC, K. 2001. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest,* 119**,** 818-823.

LEY, S., LEY-ZAPOROZHAN, J., PITTON, M. B., SCHNEIDER, J., WIRTH, G. M., MAYER, E., DUBER, C. & KREITNER, K. F. 2012. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of

vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). *Eur Radiol,* 22**,** 607-16.

MADANI, M. M. 2016. Surgical Treatment of Chronic Thromboembolic Pulmonary Hypertension: Pulmonary Thromboendarterectomy. *Methodist Debakey Cardiovasc J,* 12**,** 213-218.

MADANI, M. M., AUGER, W. R., PRETORIUS, V., SAKAKIBARA, N., KERR, K. M., KIM, N. H., FEDULLO, P. F. & JAMIESON, S. W. 2012. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. *Ann Thorac Surg,* 94**,** 97-103; discussion 103.

MAYER, E., JENKINS, D., LINDNER, J., D'ARMINI, A., KLOEK, J., MEYNS, B., ILKJAER, L. B., KLEPETKO, W., DELCROIX, M., LANG, I., PEPKE-ZABA, J., SIMONNEAU, G. & DARTEVELLE, P. 2011. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *J Thorac Cardiovasc Surg,* 141**,** 702-10.

MCGOON, M. D. & MILLER, D. P. 2012. REVEAL: a contemporary US pulmonary arterial hypertension registry. *Eur Respir Rev,* 21**,** 8-18.

MINIATI, M., MONTI, S., BOTTAI, M., SCOSCIA, E., BAULEO, C., TONELLI, L., DAINELLI, A. & GIUNTINI, C. 2006. Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism. *Medicine,* 85**,** 253-262.

MIZOGUCHI, H., OGAWA, A., MUNEMASA, M., MIKOUCHI, H., ITO, H. & MATSUBARA, H. 2012. Refined Balloon Pulmonary Angioplasty for Inoperable Patients with Chronic Thromboembolic Pulmonary Hypertension. *Circulation-Cardiovascular Interventions,* 5**,** 748-755.

MORADI, F., MORRIS, T. A. & HOH, C. K. 2019. Perfusion Scintigraphy in Diagnosis and Management of Thromboembolic Pulmonary Hypertension. *Radiographics,* 39**,** 169-185.

MOSER, K. M. & BRAUNWALD, N. S. 1973. Successful surgical intervention in severe chronic thromboembolic pulmonary hypertension. *Chest,* 64**,** 29-35.

MUTLU, B. 2017. *Thromboembolic Prophylaxis with Rivaroxaban in Patients with Chronic Thromboembolic Pulmonary hypertension: A Single Tertiary Care Center Experience from Istanbul, Turkey,* PVRI.

NIERLICH, P., HOLD, A. & RISTL, R. 2016. Outcome after surgical treatment of chronic thromboembolic pulmonary hypertension: dealing with different patient subsets. A single-centre experience. *Eur J Cardiothorac Surg,* 50**,** 898-906.

PENGO, V., LENSING, A. W. A., PRINS, M. H., MARCHIORI, A., DAVIDSON, B. L., TIOZZO, F., ALBANESE, P., BIASIOLO, A., PEGORARO, C., ILICETO, S., PRANDONI, P., RAZZOLINI, R., RAMONDO, A., BELLOTTO, F., NOVENTA, F., VILLANOVA, C., BARBERO, F., CASARA, D., NANTE, G., TORMENE, D., GEROSA, G., TESTOLIN, L., BOTTIO, T., PIOVELLA, F., VIGANO, M., D'ARMINI, A. & HYPERTENS, T. P. 2004. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *New England Journal of Medicine,* 350**,** 2257-2264.

PEPKE-ZABA, J., DELCROIX, M., LANG, I., MAYER, E., JANSA, P., AMBROZ, D., TREACY, C., D'ARMINI, A. M., MORSOLINI, M., SNIJDER, R., BRESSER, P., TORBICKI, A., KRISTENSEN, B., LEWCZUK, J., SIMKOVA, I., BARBERA, J. A., DE PERROT, M., HOEPER, M. M., GAINE, S., SPEICH, R., GOMEZ-SANCHEZ, M. A., KOVACS, G., HAMID, A. M., JAIS, X. & SIMONNEAU, G. 2011. Chronic Thromboembolic Pulmonary Hypertension (CTEPH) Results From an International Prospective Registry. *Circulation,* 124**,** 1973-1981.

PEPKE-ZABA, J., HOEPER, M. M. & HUMBERT, M. 2013a. Chronic thromboembolic pulmonary hypertension: advances from bench to patient management. *European Respiratory Journal,* 41**,** 8-9.

PEPKE-ZABA, J., JANSA, P., KIM, N. H., NAEIJE, R. & SIMONNEAU, G. 2013b. Chronic thromboembolic pulmonary hypertension: role of medical therapy. *Eur Respir J,* 41**,** 985-90.

PLANQUETTE, B., SANCHEZ, O., MARSH, J. J., CHILES, P. G., EMMERICH, J., LE GAL, G., MEYER, G., WOLFSON, T., GAMST, A. C., MOORE, R. E., GUGIU, G. B. & MORRIS, T. A. 2018. Fibrinogen and the prediction of residual obstruction manifested after pulmonary embolism treatment. *Eur Respir J,* 52.

PONNABERANAM A. 2015. Pulmonary endarterectomy (PEA) at Papworth Hospital: Discharge information.

QUARCK, R., WYNANTS, M., VERBEKEN, E., MEYNS, B. & DELCROIX, M. 2015. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. *Eur Respir J,* 46**,** 431-43.

RAJARAM, S., SWIFT, A. J., CAPENER, D., TELFER, A., DAVIES, C., HILL, C., CONDLIFFE, R., ELLIOT, C., HURDMAN, J., KIELY, D. G. & WILD, J. M. 2012. Diagnostic accuracy of contrast-enhanced MR angiography and unenhanced proton MR imaging compared with CT pulmonary angiography in chronic thromboembolic pulmonary hypertension. *European Radiology,* 22**,** 310-317.

RAJARAM, S., SWIFT, A. J., TELFER, A., HURDMAN, J., MARSHALL, H., LORENZ, E., CAPENER, D., DAVIES, C., HILL, C., ELLIOT, C., CONDLIFFE, R., WILD, J. M. & KIELY, D. G. 2013. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. *Thorax,* 68**,** 677-678.

REICHENBERGER, F., VOSWINCKEL, R., ENKE, B., RUTSCH, M., EL FECHTALI, E., SCHMEHL, T., OISCHEWSKI, H., SCHERMULY, R., WEISSMANN, N., GHOFRANI, H. A., GRIMMINGER, F., MAYER, E. & SEEGER, W. 2007. Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension. *European Respiratory Journal,* 30**,** 922-927.

REMY-JARDIN, M., RYERSON, C. J., SCHIEBLER, M. L., LEUNG, A. N. C., WILD, J. M., HOEPER, M. M., ALDERSON, P. O., GOODMAN, L. R., MAYO, J., HARAMATI, L. B., OHNO, Y., THISTLETHWAITE, P., VAN BEEK, E. J. R., KNIGHT, S. L., LYNCH, D. A., RUBIN, G. D. & HUMBERT, M. 2021. Imaging of pulmonary hypertension in adults: a position paper from the Fleischner Society. *Eur Respir J,* 57.

RIEDEL M, S. V., WIDIMSKY J, PREROVSKY I 1982. Long term follow-up of patients with pulmonary thromboembolism :late prognosis and evolution of haemodynamic and respiratory data. *Chest,* 81**,** 151-158.

ROSE, F., HATTAR, K., GAKISCH, S., GRIMMINGER, F., OLSCHEWSKI, H., SEEGER, W., TSCHUSCHNER, A., SCHERMULY, R. T., WEISSMANN, N., HANZE, J., SIBELIUS, U. & GHOFRANI, H. A. 2003. Increased neutrophil mediator release in patients with pulmonary hypertension--suppression by inhaled iloprost. *Thromb Haemost,* 90**,** 1141-9.

SAOUTI, N., DE MAN, F., WESTERHOF, N., BOONSTRA, A., TWISK, J., POSTMUS, P. E. & NOORDEGRAAF, A. V. 2009a. Predictors of mortality in inoperable chronic thromboembolic pulmonary hypertension. *Respiratory Medicine,* 103**,** 1013-1019.

SAOUTI, N., MORSHUIS, W. J., HEIJMEN, R. H. & SNIJDER, R. J. 2009b. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a single institution experience. *Eur J Cardiothorac Surg,* 35**,** 947-52; discussion 952.

SATOH, T., SATOH, K., YAOITA, N., KIKUCHI, N., OMURA, J., KUROSAWA, R., NUMANO, K., AL-MAMUN, E., SIDDIQUE, M. A., SUNAMURA, S., NOGI, M., SUZUKI, K., MIYATA, S., MORSER, J. & SHIMOKAWA, H. 2017. Activated TAFI Promotes the Development of Chronic Thromboembolic Pulmonary Hypertension: A Possible Novel Therapeutic Target. *Circ Res,* 120**,** 1246-1262.

SHERRICK, A. D., SWENSEN, S. J. & HARTMAN, T. E. 1997. Mosaic pattern of lung attenuation on CT scans: Frequency among patients with pulmonary artery hypertension of different causes. *American Journal of Roentgenology,* 169**,** 79-82.

SIMONNEAU 2013. Long-Term Outcome Of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results Of An International Prospective Registry Comparing Operated Versus Non Operated Patients. *AFRCCM***,** A5365.

SIMONNEAU 2014. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH): 2-year results from the CHEST-2 long-term extension. *Eur Respir J* Abstract number 1802.

SIMONNEAU, G., D'ARMINI, A. M., GHOFRANI, H. A., GRIMMINGER, F., JANSA, P., KIM, N. H., MAYER, E., PULIDO, T., WANG, C., COLORADO, P., FRITSCH, A., MEIER, C., NIKKHO, S. & HOEPER, M. M. 2016. Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomised, long-term extension trial. *Lancet Respir Med,* 4**,** 372-80.

SKORO-SAJER, N., MARTA, G., GERGES, C., HLAVIN, G., NIERLICH, P., TAGHAVI, S., SADUSHI-KOLICI, R., KLEPETKO, W. & LANG, I. M. 2014. Surgical specimens, haemodynamics and long-term outcomes after pulmonary endarterectomy. *Thorax,* 69**,** 116-122.

SOON, E., HOLMES, A. M., TREACY, C. M., DOUGHTY, N. J., SOUTHGATE, L., MACHADO, R. D., TREMBATH, R. C., JENNINGS, S., BARKER, L., NICKLIN, P., WALKER, C., BUDD, D. C., PEPKE-ZABA, J. & MORRELL, N. W. 2010. Elevated Levels of Inflammatory Cytokines Predict Survival in Idiopathic and Familial Pulmonary Arterial Hypertension. *Circulation,* 122**,** 921-U90.

SOUTHWOOD, M., MACKENZIE ROSS, R. V., KUC, R. E., HAGAN, G., SHEARES, K. K., JENKINS, D. P., GODDARD, M., DAVENPORT, A. P. & PEPKE-ZABA, J. 2016. Endothelin ETA receptors predominate in chronic thromboembolic pulmonary hypertension. *Life Sci,* 159**,** 104-110.

SUDA, R., TANABE, N., ISHIDA, K., KATO, F., URUSHIBARA, T., SEKINE, A., NISHIMURA, R., JUJO, T., SUGIURA, T., SHIGETA, A., SAKAO, S. & TATSUMI, K. 2017. Prognostic and pathophysiological marker for patients with

chronic thromboembolic pulmonary hypertension: Usefulness of diffusing capacity for carbon monoxide at diagnosis. *Respirology,* 22**,** 179-186.

SUNTHARALINGAM, J., MACHADO, R. D., SHARPLES, L. D., TOSHNER, M. R., SHEARES, K. K., HUGHES, R. J., JENKINS, D. P., TREMBATH, R. C., MORRELL, N. W. & PEPKE-ZABA, J. 2007. Demographic features, BMPR2 status and outcomes in distal chronic thromboembolic pulmonary hypertension. *Thorax,* 62**,** 617-622.

SUNTHARALINGAM, J., TREACY, C. M., DOUGHTY, N. J., GOLDSMITH, K., SOON, E., TOSHNER, M. R., SHEARES, K. K., HUGHES, R., MORRELL, N. W. & PEPKE-ZABA, J. 2008. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest,* 134**,** 229-236.

SUNTHARALINGAM, J. M. R., R. ROBINSON, G. HALL, T. HUDSON, B. REDMAN, S. GRAHAM, R. LITTLE, D. EASAW, J. AUGUSTINE, D. CARSON, D. COGHLAN, J. 2018. Chronic thromboembolic pulmonary hypertension (CTEPH) – is it chronically underdiagnosed? *Thorax,* 73.

TABOADA, D., PEPKE-ZABA, J., JENKINS, D. P., BERMAN, M., TREACY, C. M., CANNON, J. E., TOSHNER, M., DUNNING, J. J., NG, C., TSUI, S. S. & SHEARES, K. K. 2014. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. *European Respiratory Journal,* 44**,** 1635-1645.

THAKRAR, M. V., A. HALL, R. CRACKETT, M. DAY, G. MAC GOWAN, J.L. LORDAN, A.J. FISHER, C. TREACEY & J. PEPKE-ZABA 2013. Functional and Quality of Life Improvements in Treated Patients with Chronic Thromboembolic Pulmonary Hypertension. *The Journal of Heart and Lung Transplantation,* 32**,** S304.

TOSHNER, M. 2016. Genetic testing in pulmonary hypertension: how should our clinical practice reflect recent advances? *Eur Respir J,* 47**,** 388-9.

TROMEUR, C., JAIS, X., MERCIER, O., COUTURAUD, F., MONTANI, D., SAVALE, L., JEVNIKAR, M., WEATHERALD, J., SITBON, O., PARENT, F., FABRE, D., MUSSOT, S., DARTEVELLE, P., HUMBERT, M., SIMONNEAU, G. & FADEL, E. 2018. Factors predicting outcome after pulmonary endarterectomy. *PLoS One,* 13**,** e0198198.

TUNARIU, N., GIBBS, S. J., WIN, Z., GIN-SING, W., GRAHAM, A., GISHEN, P. & AL-NAHHAS, A. 2007. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med,* 48**,** 680-4.

WILKENS, H., KONSTANTINIDES, S., LANG, I. M., BUNCK, A. C., GERGES, M., GERHARDT, F., GRGIC, A., GROHE, C., GUTH, S., HELD, M., HINRICHS, J. B., HOEPER, M. M., KLEPETKO, W., KRAMM, T., KRUGER, U., LANKEIT, M., MEYER, B. C., OLSSON, K. M., SCHAFERS, H. J., SCHMIDT, M., SEYFARTH, H. J., ULRICH, S., WIEDENROTH, C. B. & MAYER, E. 2018. Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations from the Cologne Consensus Conference 2018. *Int J Cardiol,* 272S**,** 69-78.

ZABINI, D., HEINEMANN, A., FORIS, V., NAGARAJ, C., NIERLICH, P., BALINT, Z., KWAPISZEWSKA, G., LANG, I. M., KLEPETKO, W., OLSCHEWSKI, H. & OLSCHEWSKI, A. 2014. Comprehensive analysis of inflammatory markers in chronic thromboembolic pulmonary hypertension patients. *Eur Respir J,* 44**,** 951-62.

Appendix

TABLES

Table S1: The table shows all the fields that are present in the new ASPIRE 2 registry database but missing in the ASPIRE 1 registry database

Number	Categories	Sub-categories
1	First clinic visit	Emphasis 10 QoL questionnaire (Y/N) Emphasis 10 QoL questionnaire Score (0-50)
2	Final clinic visit	Emphasis 10 QoL questionnaire (Y/N) Emphasis 10 QoL questionnaire Score (0-50)
3	Presenting symptoms	Duration of symptoms Shortness of breath (Y/N) Chest pain (Y/N) Palpitations (Y/N) Presyncope (Y/N) Syncope (Y/N) Cough (Y/N) Haemoptysis (Y/N) Ankle swelling (Y/N) Calf pain (Y/N) Tiredness (Y/N) others
4	Risk factors for CTEPH	History of DVT and PE (Y/N) History of IVC filter insertion for PE (Y/N) Previous major surgery (Y/N) Varicose vein (Y/N) Obesity (Y/N) Chronic venous insufficiency (Y/N) Prolonged immobilization (Y/N) Chronic osteomyelitis (Y/N) History of cancer (Y/N) Coronary artery disease (Y/N) Thyroid disorder (Y/N) History of fracture (Y/N) NIDDM (Y/N) IDDM (Y/N) CCF(Y/N) History of infected VA shunt/PPM (Y/N)
5	Imaging modalities	Q-scan(Y/N) Date of Q-scan VQ Scan (Y/N) Date of VQ scan CTPA (Y/N) Date of CTPA MRA with perfusion mapping (Y/N) Date of test Formal pulmonary angiography (Y/N) Date of test

Number	Categories	Sub-categories
6	Blood tests	Haemoglobin Ferritin Creatinine Albumin White blood cell Neutrophil Platelets CRP (Y/N) Date of test Result
7	Pulmonary function test (first)	FEV1/FVC
8	Pulmonary function test (final)	FEV1/FVC
9	Right heart catheter (first)	TPR
10	Right heart catheter (final)	TPR
11	Cardiac MRI (first)	C-MRI (Y/N) Date of C-MRI Size of aorta PA size LVEDV LVEF (%) LVEDVI LVESVI SV SVI HR CO CI RVEDV RVESV RVEF (%) RVEDVI RVESVI
12	Cardiac MRI (final)	C- MRI (Y/N) Date of C-MRI Size of aorta PA size LVEDV LVEF (%) LVEDVI LVESVI SV SVI HR CO CI RVEDV RVESV RVEF (%) RVEDVI RVESVI
13	Pulmonary endarterectomy	Date of referral for PEA surgery

Number	Categories	Sub-categories
14	IVC filter insertion	Date of IVC filter insertion
15	Bridging therapy	Presurgical treatment given at the time of endarterctomy (Y/N) Sildenafil Tadalafil Bosentan Ambrisentan Macitentan Iloprost Nebs Iloprosti/v
16	Final diagnosis	CTEPH-surgical-operated CTEPH-surgical-not operated CTEPH-non-surgical CTED

Definition of abbreviation: QoL= quality of life; DVT= deep vein thrombosis; PE= pulmonary embolism; IVC=inferior vena cava; NIDDM= non-insulin dependent diabetes mellitus; IDDM= insulin dependent diabetes mellitus; CCF= congestive cardiac failure; Q=perfusion; VQ= ventilation perfusion; CTPA=computed tomography pulmonary angiogram; MRA= magnetic resonance angiogram; CRP= C reactive protein; FEV1=forced expiratory volume at 1st second; FVC= forced vital capacity; TPR= total pulmonary resistance; C-MRI= cardiac magnetic resonance imaging; PA=pulmonary artery; LVEDV= left ventricular end diastolic volume; LVEF=left ventricular ejection fraction; LVEDVI=left ventricular end diastolic volume index; LVESVI=left ventricular end systolic volume index; SV=stroke volume; SVI=stroke volume index; HR=heart rate; CO=cardiac output; CI=cardiac index; RVEDV=right ventricular end diastolic volume; RVESV=right ventricular end systolic volume; RVEF= right ventricular ejection fraction; RVEDVI= right ventricular end diastolic volume index; RVESVI= right ventricular end systolic volume index; PEA= pulmonary endarterectomy; CTEPH= chronic thromboembolic pulmonary hypertension; CTED= chronic thromboembolic disease;

Table S2: The following variables were used in the cox regression analysis for survival during univariate analysis in the CTEPH-whole cohort, CTEPH-surgical-operated, CTEPH-surgical-not-operated (including unfit for surgery and patient choice) and CTEPH-non-surgical-disease distribution groups

Age	History of fracture	Serum Creatinine
Gender	Hypertension	Serum Albumin
History of VTE	History of smoking	White blood cells
History of thrombolysis for PE	Family history of VTE	Neutrophil
Thrombophilic disorders	Duration of symptoms	Platelets
Antiphospholipid syndrome	Syncope	C-reactive protein
History of splenectomy	Ankle swelling	mPAP
History of IBD	Chest pain	Change in mPAP
History of infected AV shunt/PPM	Palpitation	Right atrial pressure
Obesity	Presyncope	Cardiac output
IDDM	Haemoptysis	Cardiac index
NIDDM	WHO FC (first)	Pulmonary vascular resistance
History of cancer	Saturation (first)	Total pulmonary resistance
Chronic venous insufficiency	Systolic Blood pressure (first)	SvO2
History of Coronary artery disease	Body mass index	LVEF (%)-first
Left ventricular failure	ISWD (first)	RVEF (%) -first
Chronic kidney disease	ISWD (final)	PH specific targeted therapy
History of bronchiectasis	Change in walk distance	Intravenous iloprost
History of asthma	FEV1(%)- first	Subcutaneous LMWH
Chronic obstructive pulmonary disease	FVC (%)-first	PEA surgery (for CTEPH-whole cohort only)
Interstitial lung disease	FEV1/FVC-first	Post-operative PVR (for CTEPH-surgical-operated only)
Sleep disordered breathing	D_{LCO} (%)-first	Persistent PH post PEA (for CTEPH-surgical-operated)
Cerebrovascular event	D_{LCO} (%)-final	Bridging therapy (for CTEPH-surgical-operated only)
Dyslipidaemia	Haemoglobin	
History of Valvular heart disease	Serum Ferritin	

Definition of abbreviations; VTE = venous thromboembolism; PE = pulmonary embolism; IBD = inflammatory bowel disease; AV = atrio-ventricular; PPM = permanent pacemaker; IDDM = insulin dependent diabetes mellitus; NIDDM = non-insulin dependent diabetes mellitus; WHO FC = World Health Organisation functional class; ISWD = incremental shuttle walk distance; FEV1 = forced expiratory volume at 1st second; FVC = forced vital capacity; D_{LCO} = diffusion capacity of lung for carbon monoxide; mPAP = mean pulmonary artery pressure; SvO2 = mixed venous oxygen saturation; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; PH = pulmonary hypertension; PEA = pulmonary endarterectomy; CTEPH = chronic thromboembolic pulmonary hypertension; PVR = pulmonary vascular resistance;

FIGURES

Figure S1: ASPIRE registry showing demographics and details of the clinic visits

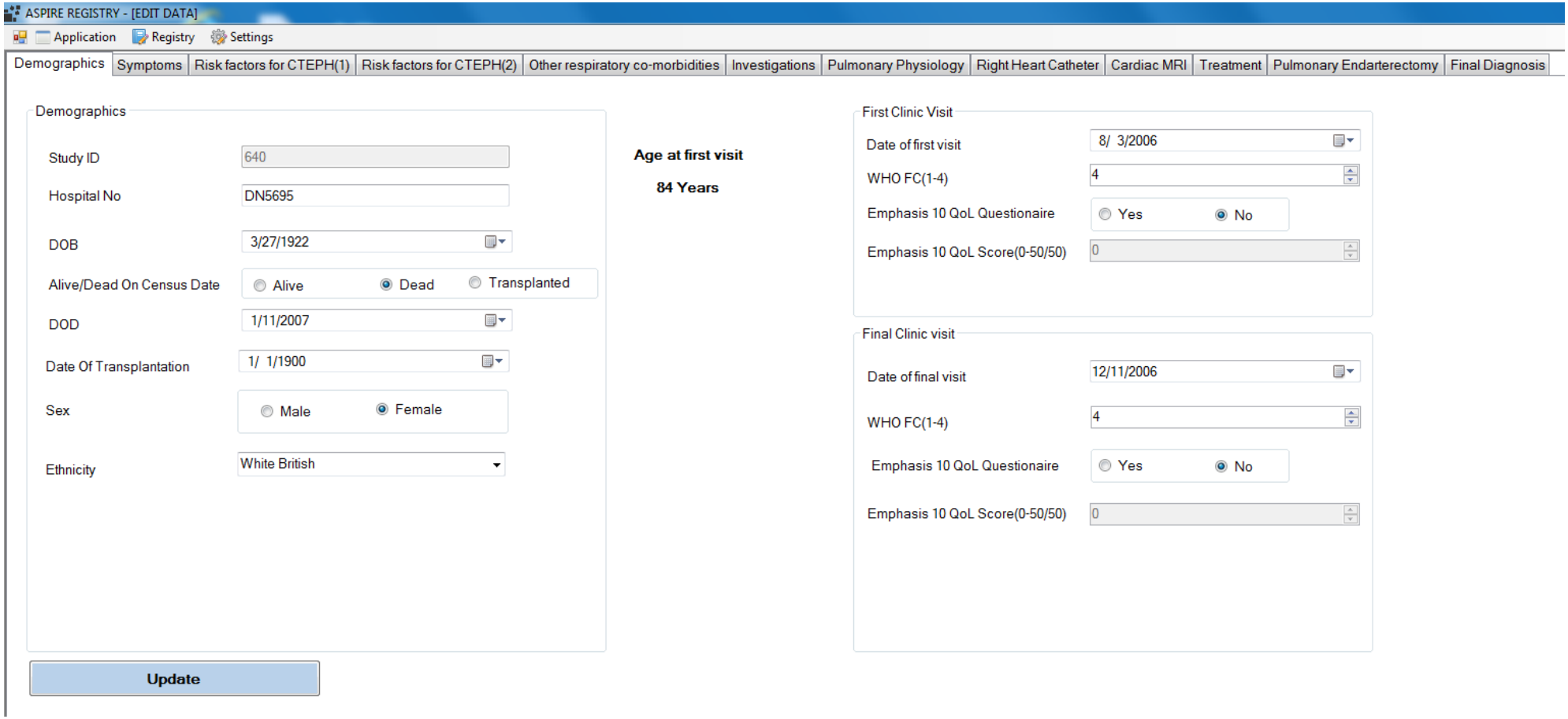


Figure S2: ASPIRE registry showing presenting symptoms

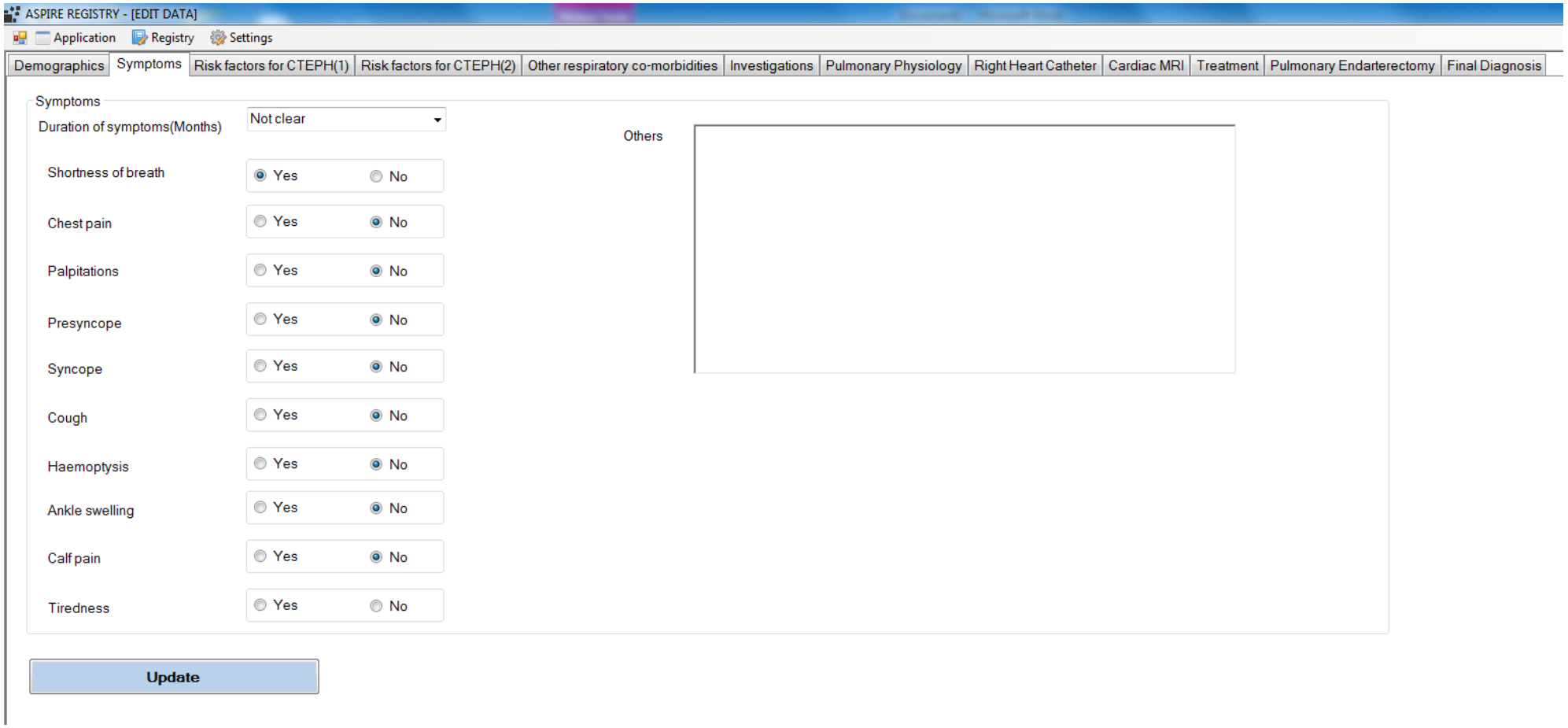


Figure S3: ASPIRE registry showing risk factors for CTEPH

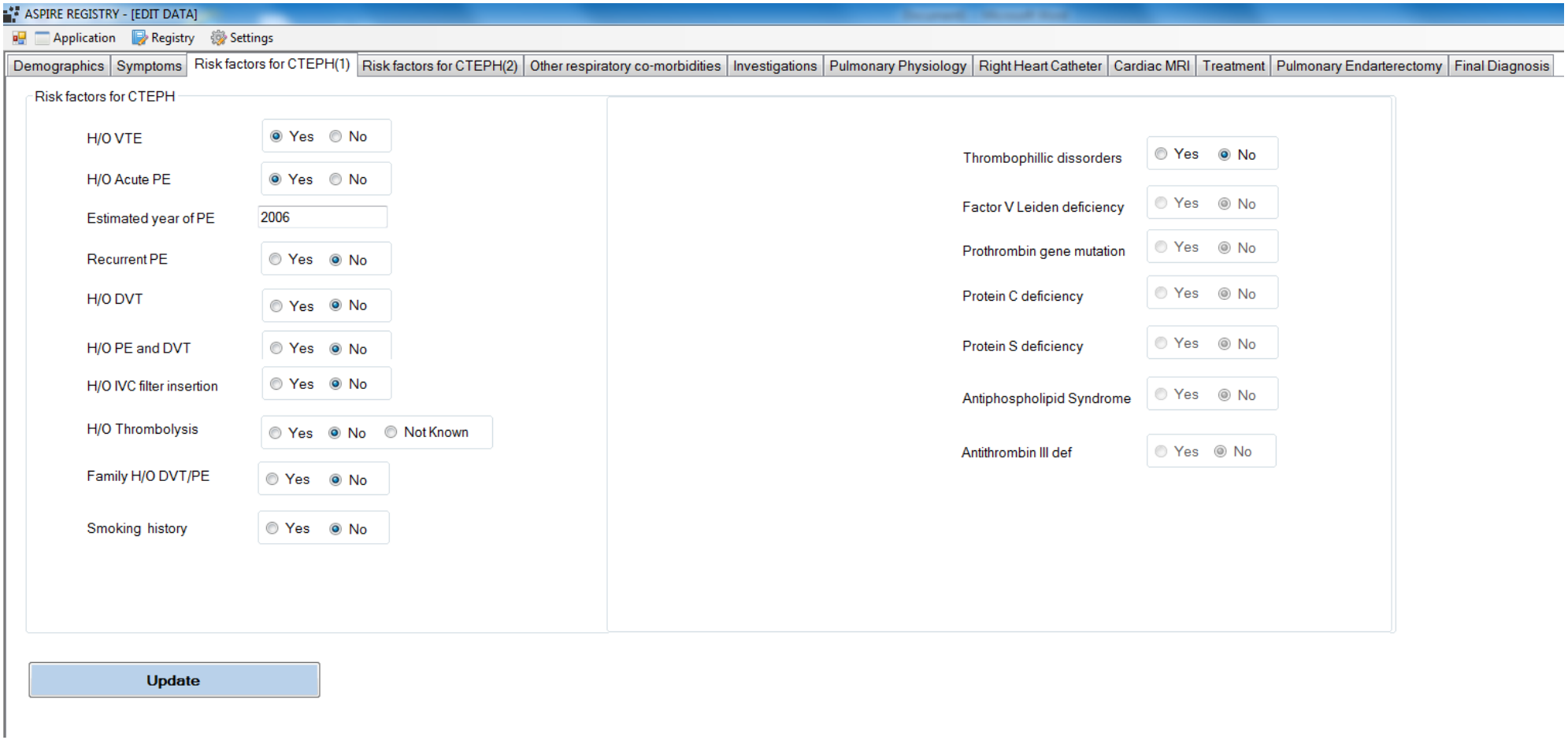


Figure S4: ASPIRE registry showing further risk factors for CTEPH

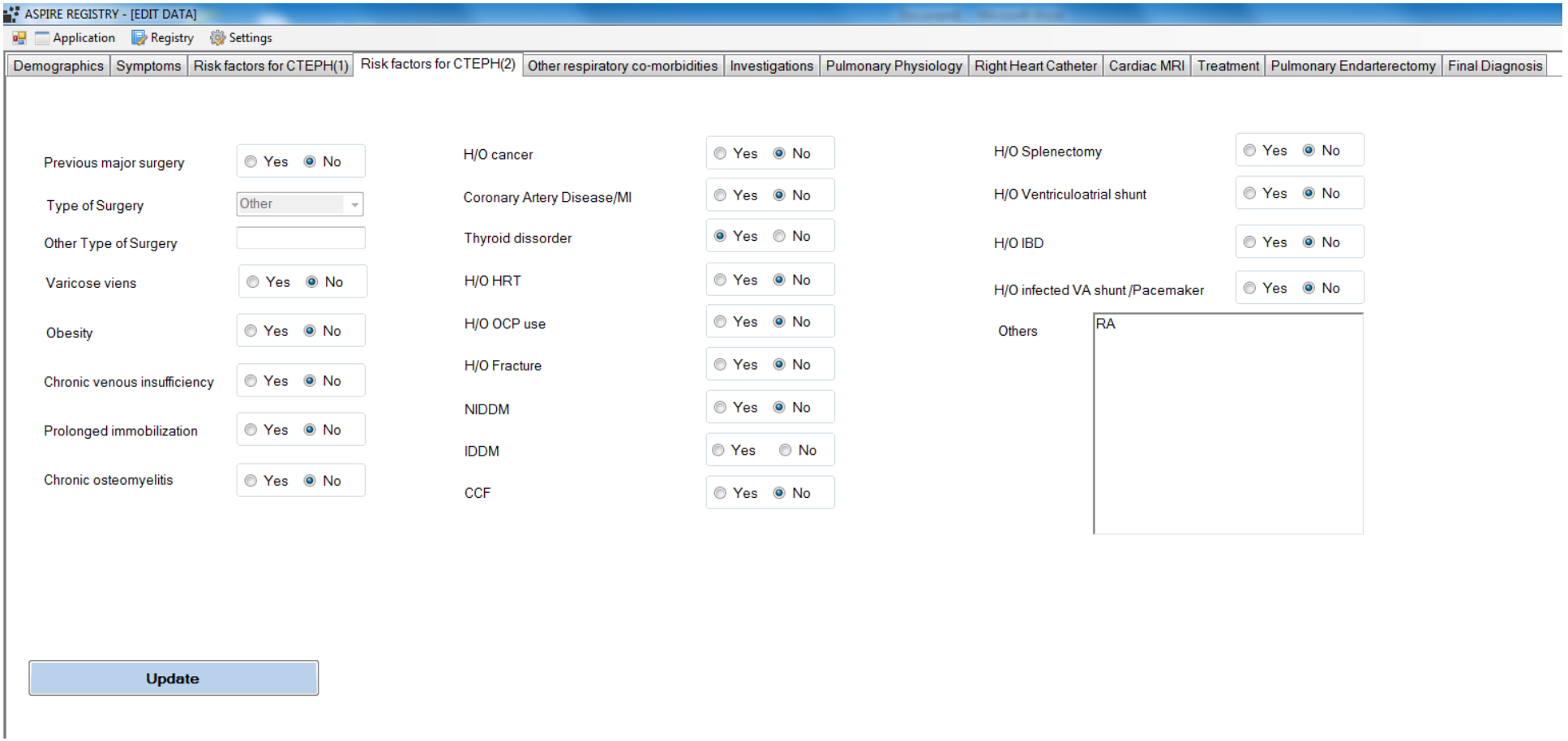


Figure S5: ASPIRE registry showing the respiratory co-morbidities

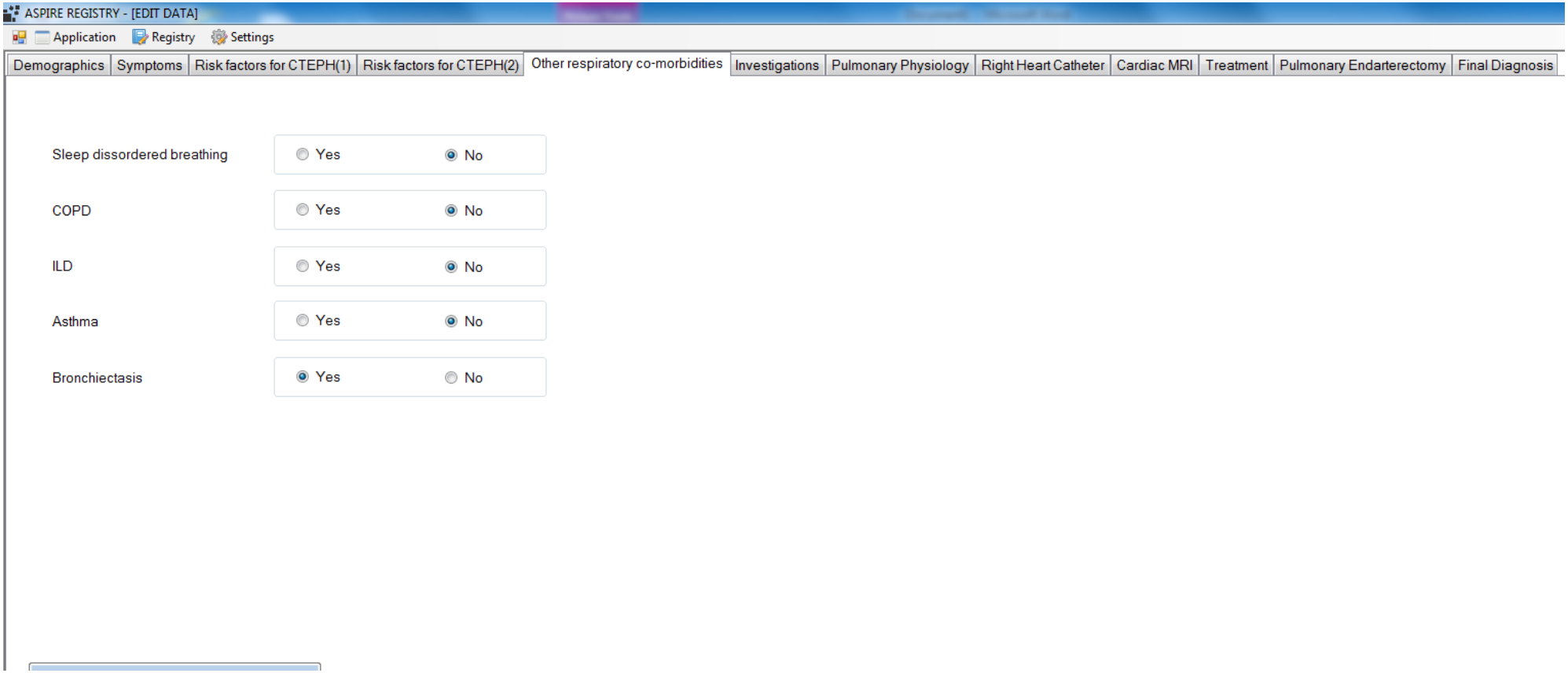


Figure S6: ASPIRE registry showing the imaging modalities and the initial blood test

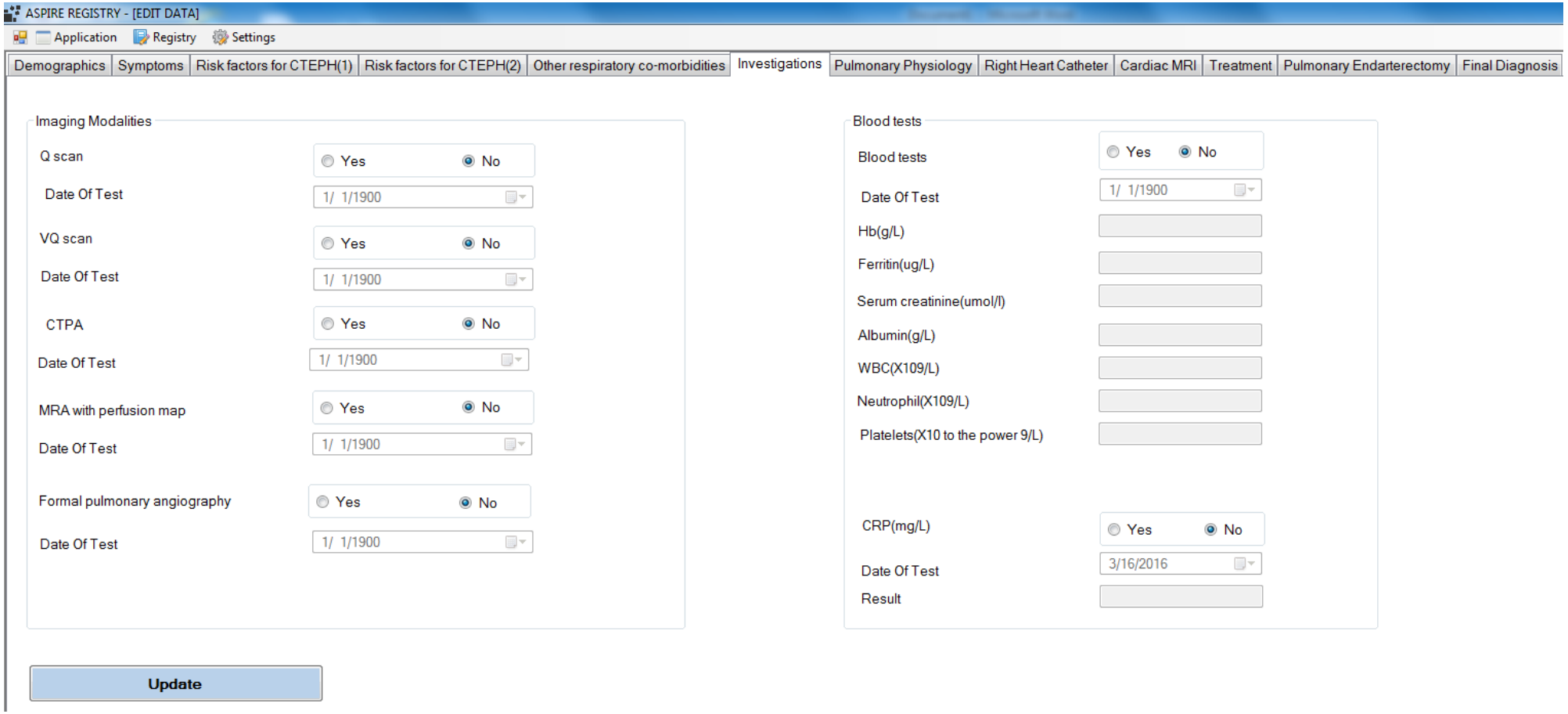


Figure S7: ASPIRE registry showing pulmonary physiology

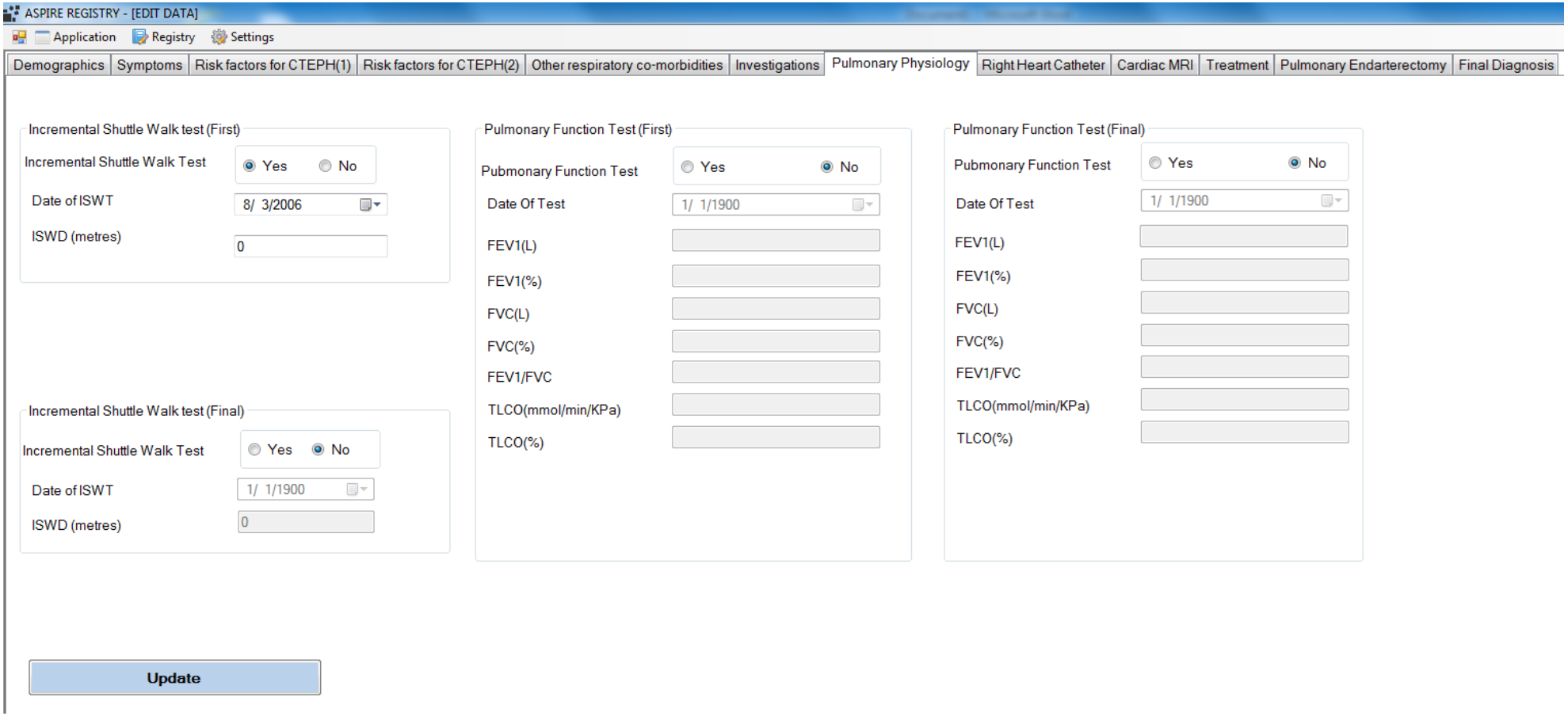


Figure S8: ASPIRE registry showing RHC data

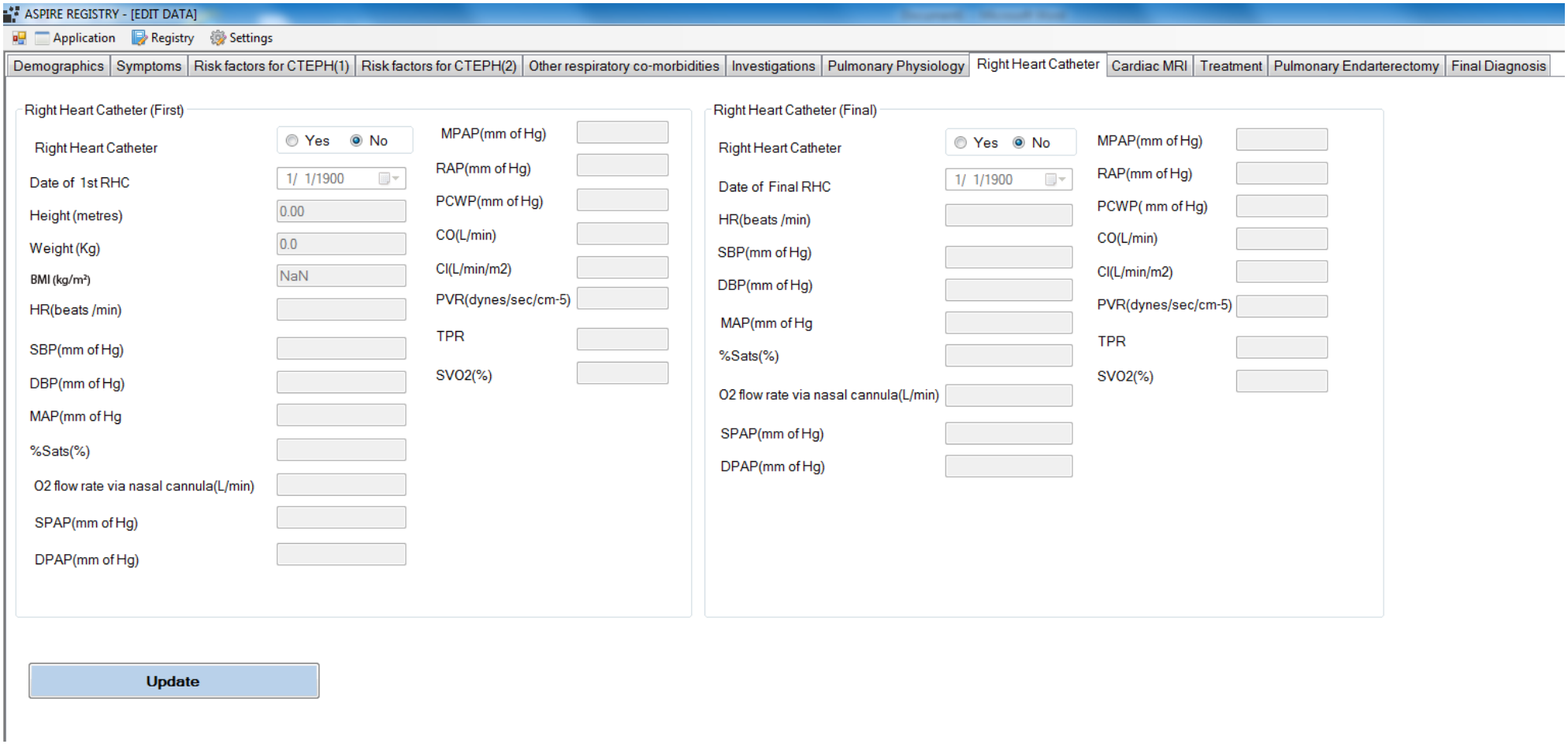


Figure S9: ASPIRE registry showing Cardiac MRI matrix data

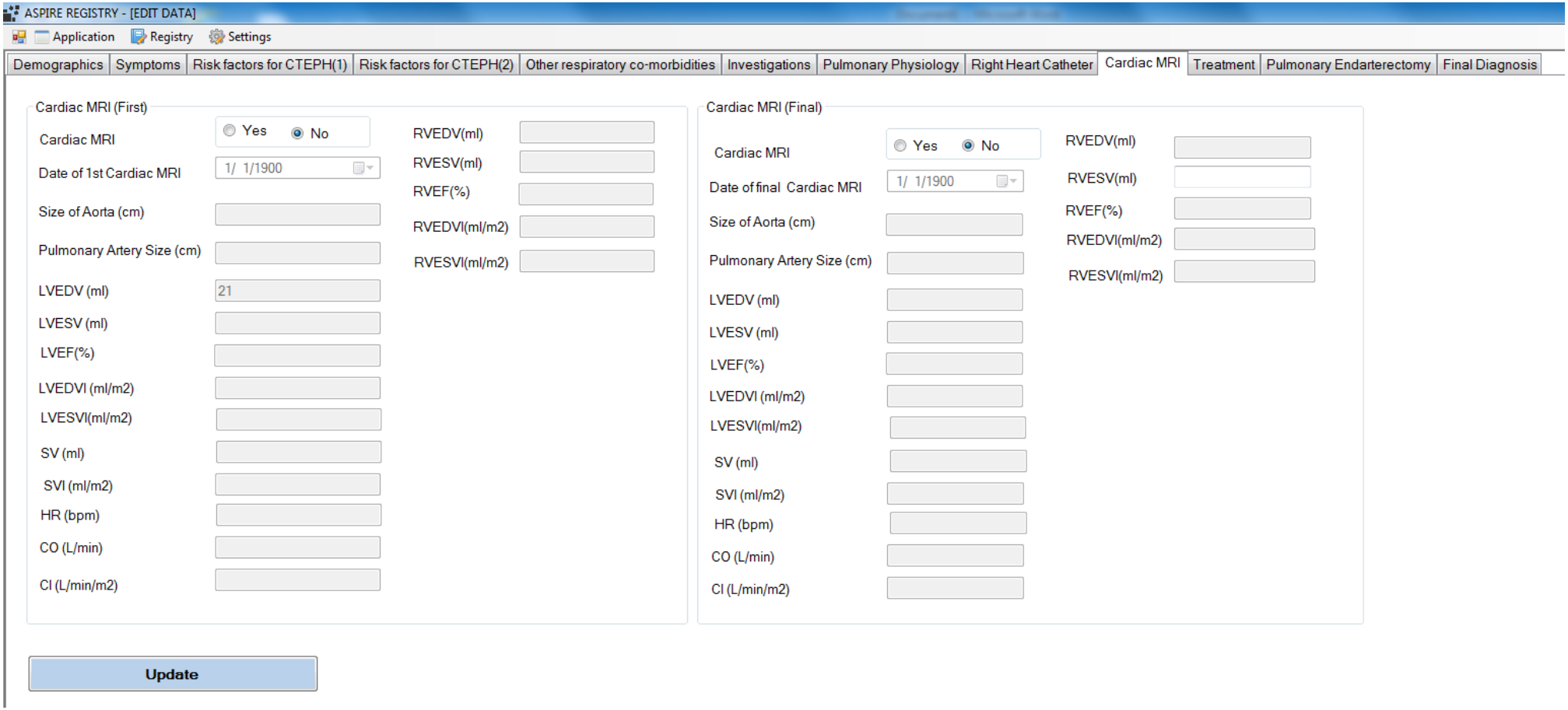


Figure S10: ASPIRE registry showing treatment with PH specific targeted therapy and anticoagulants

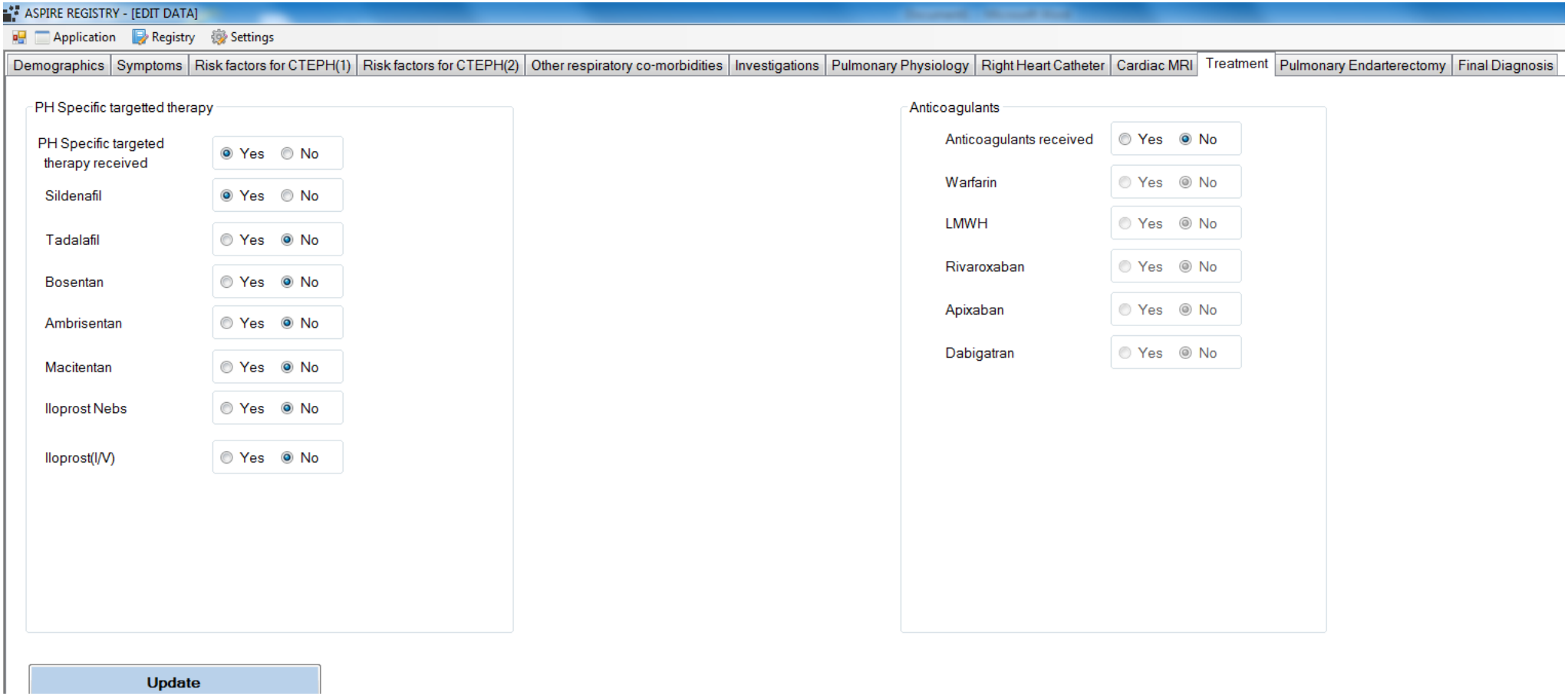


Figure S11: ASPIRE registry showing Pulmonary endarterectomy, IVC filter insertion & bridging therapy in patients with CTEPH

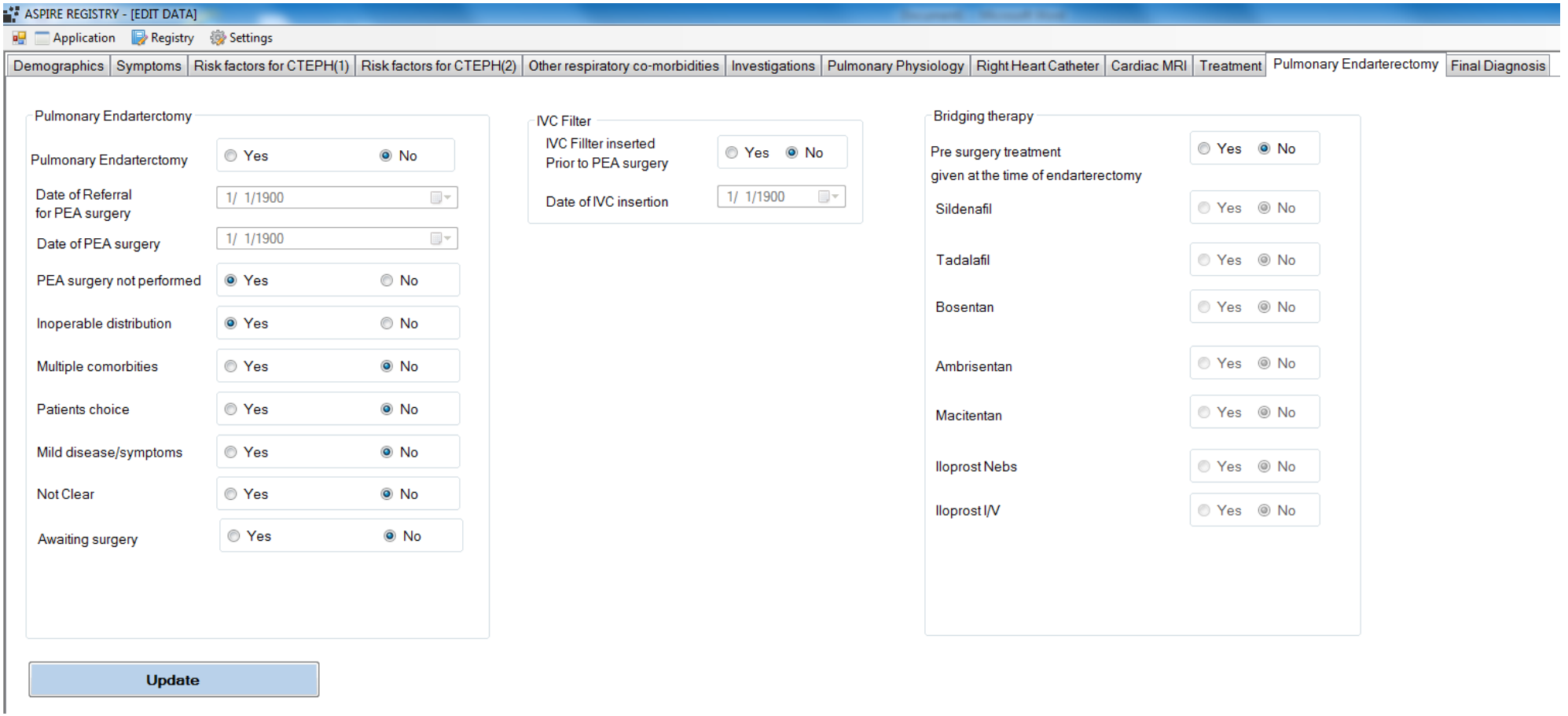


Figure S12: ASPIRE registry showing the final diagnosis