TITLE: Demographics, BMPR2 status and outcomes in Distal Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT

Rationale
Although pulmonary endarterectomy (PEA) is potentially curative in Chronic Thromboembolic Pulmonary Hypertension (CTEPH), some patients have distally distributed disease that is not amenable to surgery. The aetiology and characteristics of this patient group are currently not well understood.

Objectives
This study compares the baseline demographics and outcomes of subjects with distal CTEPH, proximal CTEPH and Idiopathic Pulmonary Arterial Hypertension (IPAH). This will help determine whether these conditions represent separate entities, or whether they in fact exist along the same spectrum of disease.

Methods
The medical history, clinical characteristics, Bone Morphogenetic Receptor type 2 (BMPR2) mutation status and outcomes of 96 IPAH, 35 distal CTEPH and 68 proximal CTEPH subjects referred to a single specialist centre between 1994 and 2005 were reviewed.

Results
There were significant differences between the distal CTEPH, proximal CTEPH and IPAH groups in age (55.9yrs vs 54.8yrs vs 46.2yrs p<0.0001), proportion who were male (43% vs 69% vs 29% p<0.0001), previous Deep Vein Thrombosis (28.6% vs 30.9% vs 3.1% p<0.0001), positive BMPR2 status (0% vs 0% vs 15% p=0.018), mean Pulmonary Artery Pressure (47.3mmHg vs 45.4mmHg vs 54.8mmHg p<0.0001) and Total Pulmonary Resistance (12.9WU vs 12.4WU vs 18.1WU p<0.0001). Both distal CTEPH and IPAH subjects were managed similarly, and had comparable survival characteristics (77% 1yr, 53% 3yrs vs 86% 1yr, 60% 3yrs p=0.68).

Conclusions
Distal and proximal CTEPH groups share certain demographic features that not only indicate a common aetiology but also help differentiate them from IPAH patients. Despite more favourable haemodynamic parameters in the distal CTEPH group, subjects displayed a poor long term outcome similar to that of IPAH subjects.
INTRODUCTION
Chronic thromboembolic pulmonary hypertension (CTEPH) is an important cause of pulmonary hypertension that is commonly considered to be the consequence of acute pulmonary embolic disease(1). Following an acute event, unresolved residual thrombus becomes organised and fibrosed, leading to ongoing obstruction to pulmonary blood flow. Untreated, this leads to progressive pulmonary hypertension, right ventricular dysfunction and death(2). Recent evidence suggests that CTEPH may be more common than originally anticipated and may complicate up to 3.8% of acute pulmonary embolic events(3). In patients with predominantly ‘proximal’ disease surgical intervention (Pulmonary Endarterectomy or PEA) can be very effective, often leading to normalisation of pulmonary arterial pressures(4). However, when the degree of haemodynamic compromise is out of proportion to the quantity of surgically accessible disease, surgery is often inappropriate(5). Pulmonary endarterectomy in these patients is less successful, and is associated with a higher mortality(6). In this inoperable or ‘distal’ disease, where the majority of organised thrombus lies beyond the subsegmental level, management has historically consisted of supportive therapy alone.

Idiopathic Pulmonary Arterial Hypertension (IPAH) is characterised by a small vessel vasculopathy that occurs in the absence of a known precipitant. A distinction has recently been made between patients with this disorder and those who have both PAH and a positive family history (Familial PAH or FPAH)(7). This follows the discovery that mutations in the Bone Morphogenetic Protein Receptor type II (BMPR2) gene underlie up to 70% of FPAH cases(8). BMPR2 mutations have also been observed in IPAH, albeit at a lower incidence(9), a proportion of which represent de novo spontaneous mutations or hitherto undiagnosed familial disease(9, 10). Histologically, IPAH is characterised not only by intimal fibrosis and plexiform lesions, but also by organised in situ thrombus(11). In situ thrombus formation in these patients can be extensive, sometimes clinically and radiologically mimicking the appearances of CTEPH(12). Moreover, in CTEPH patients peripheral IPAH-like vasculopathic changes have been demonstrated that co-exist with the more upstream obstructive thrombotic lesions already described(13). These shared histological features have therefore led to the suggestion that IPAH and CTEPH may represent a continuum of disease, thus casting doubt over the presumed embolic aetiology of CTEPH(14, 15). In such a model, distal CTEPH could represent an overlap condition, displaying characteristics of both IPAH and proximal CTEPH.

There is a paucity of information available on the characteristics of patients with distal CTEPH, particularly in comparison to proximal CTEPH and IPAH patients. Most studies have combined data on distal and proximal CTEPH patients, on the presumption that the two conditions represent the same disease entity(2, 16). This study compares the baseline demographics and outcomes of subjects with IPAH, distal CTEPH and proximal CTEPH to help characterise the aetiology of each of these conditions further. This will also help determine whether these conditions represent separate entities, or whether they in fact exist along the same spectrum of disease.

METHODS
Subjects
The study was undertaken at the Pulmonary Vascular Diseases Unit (PVDU), Papworth Hospital, one of five specialist Pulmonary Hypertension centres in the United Kingdom, and the national referral centre for PEA surgery. All consecutive patients referred with IPAH or CTEPH between 1994 and 2005 were identified. All had been diagnosed with pulmonary hypertension at right heart catheterisation using standard diagnostic criteria(7). All subjects underwent a standardised imaging protocol that is published elsewhere(17). This relies primarily on multislice CT pulmonary angiography (CTPA) and High Resolution CT (HRCT) to distinguish between patients with CTEPH and IPAH, using a 32-slice CT scanner. The
use of CTPA in diagnosing thromboembolic obstruction has previously been validated against catheter directed pulmonary angiography(18). Moreover, HRCT has also been shown to be as sensitive as and more specific than radionucleide scanning in the differentiation of CTEPH from IPAH(19).

Once identified, subjects with CTEPH were further characterised through a combination of catheter directed pulmonary angiography and/or contrast enhanced MR pulmonary angiography, to assess for operability. All imaging was reviewed by a panel of specialist physicians, radiologists and surgeons who determined the distribution of disease. Only subjects with distal disease (ie disease where thrombotic lesions were situated predominantly or exclusively beyond the subsegmental level) were included for analysis in the distal group, thus excluding patients who were inoperable for reasons other than disease distribution alone. Subjects were only included in the proximal group if they had undergone PEA surgery and demonstrated normalisation of their pulmonary artery pressures (ie mean PAP<25mmHg) at their three month post-operative assessment - this approach was taken to exclude subjects with co-existing proximal and distal disease. DNA was obtained from subjects in all three groups, where available, and analysed for the presence of BMPR2 mutations by direct fluorescent sequencing on an ABI3730 using previously described primers and conditions(8).

Approval to conduct the study was granted from the local review board. Ethical approval was granted and patient consent obtained prior to testing for BMPR2 mutations.

Data collection
Baseline demographic data were obtained by retrospective case note review. Subjects were only deemed to have had a prior thromboembolic event (TED) if a Deep Vein Thrombosis (DVT) or Pulmonary Embolus (PE) had been demonstrated on appropriate imaging (ie Doppler leg ultrasound or venography for DVT and VQ scanning or CTPA for PE) more than six months prior to referral and managed appropriately with formal anticoagulation. Data were also collected on the presence of established risk factors for CTEPH, including splenectomy, the presence of a ventriculo-atrial (VA) shunt, osteomyelitis and inflammatory bowel disease (IBD)(20). Subjects were considered to have received targeted medical therapy if they had been prescribed prostanoid therapy, an endothelin receptor antagonist or a phosphodiesterase inhibitor during their follow up period.

Statistical analysis
All eligible patients from this centre were studied. Continuous variables are summarised as the mean and standard deviation (SD). Normally distributed variables were compared between groups using a one-way ANOVA followed by post-hoc pair-wise comparisons for significant differences using Bonferroni corrections. Categorical variables were summarised as the percentage of the total studied and compared using the chi-square test, or Fisher’s exact test whenever low expected cell counts were encountered. Data were complete with the exception of BMPR2 status. Survival rates from presentation at the specialist centre were estimated using Kaplan-Meier methods, treating death as an event and censoring all other subjects at the end of follow up or at transplantation, whichever occurred first. A comparison of survival between the distal CTEPH and IPAH groups was made using a log-rank test.

All analyses were performed using SPSS v12 software. Statistical significance refers to a p-value less than 5%.

RESULTS
Baseline characteristics
The inclusion criteria for the study were fulfilled by 199 subjects, of whom 96 had IPAH, 35 had distal CTEPH and 68 had proximal CTEPH. BMPR2 mutation status was available in 90
subjects (45%). A comparison of baseline characteristics is shown in Table 1. The IPAH group were significantly younger and significantly less likely to have had a previous thromboembolic event compared with both distal and proximal CTEPH groups. The proportion of males was significantly higher in proximal CTEPH compared with either IPAH or distal CTEPH. The prevalence of splenectomy also significantly differed between the three populations, with the highest prevalence occurring in the distal CTEPH group. There was no difference in incidence of VA shunt, osteomyelitis or IBD between groups.

The distribution of BMPR2 mutations was significantly different between the three groups. Mutations were present in 15% of IPAH subjects but were not observed in either the distal CTEPH or proximal CTEPH groups.

Table 1: Baseline characteristics of IPAH, distal CTEPH and proximal CTEPH groups

<table>
<thead>
<tr>
<th></th>
<th>IPAH (n=96)</th>
<th>Distal CTEPH (n=35)</th>
<th>Proximal CTEPH (n=68)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)*</td>
<td>46.2 (16.9)</td>
<td>55.9 (13.1)</td>
<td>54.8 (14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender†</td>
<td>29%</td>
<td>43%</td>
<td>69%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean BMI in kg/m² (SD)</td>
<td>27.1 (5.8)</td>
<td>27.9 (7.5)</td>
<td>27.4 (3.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>Positive BMPR2 status‡</td>
<td>15% (n=40)</td>
<td>0% (n=25)</td>
<td>0% (n=25)</td>
<td>0.018</td>
</tr>
<tr>
<td>Prior TED§</td>
<td>5.2%</td>
<td>74.3%</td>
<td>75%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior DVT</td>
<td></td>
<td></td>
<td>3.1%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Previous splenectomy**</td>
<td>3.1%</td>
<td>11.4%</td>
<td>1.6%</td>
<td>0.042</td>
</tr>
<tr>
<td>Positive smoking history</td>
<td>47.9%</td>
<td>65.7%</td>
<td>50%</td>
<td>0.18</td>
</tr>
<tr>
<td>WHO functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>20 (21%)</td>
<td>10 (29%)</td>
<td>11 (16%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>50 (53%)</td>
<td>17 (49%)</td>
<td>32 (47%)</td>
<td>0.37</td>
</tr>
<tr>
<td>IV</td>
<td>24 (26%)</td>
<td>8 (22%)</td>
<td>25 (37%)</td>
<td></td>
</tr>
<tr>
<td>Mean 6 Minute Walk distance in metres (SD)</td>
<td>257 (118)</td>
<td>254 (99)</td>
<td>256 (131)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Significant pairwise comparisons are listed below:
*p=0.005 IPAH vs proximal CTEPH; p=0.002 IPAH vs distal CTEPH
†p<0.001 IPAH vs proximal CTEPH; p=0.04 proximal CTEPH vs distal CTEPH
‡p=0.046 IPAH vs proximal CTEPH; p=0.046 IPAH vs distal CTEPH
§p=0.001 IPAH vs proximal CTEPH; p<0.001 IPAH vs distal CTEPH
||p<0.001 IPAH vs proximal CTEPH; p<0.001 IPAH vs distal CTEPH
**p=0.026 proximal vs distal CTEPH

Table 2 summarises haemodynamic and pulmonary function for the 3 groups. Mean Pulmonary Artery Pressure (mPAP) and Total Pulmonary Resistance (TPR) were significantly higher in the IPAH group compared with both distal and proximal CTEPH groups. Diffusing capacity for carbon monoxide (TLCO) was significantly higher in proximal CTEPH compared with either IPAH or distal CTEPH. KCO was significantly higher in proximal CTEPH than in IPAH. Forced Vital Capacity (FVC) was lower in distal CTEPH than in proximal CTEPH.
Table 2: Baseline haemodynamics and spirometry of IPAH, distal CTEPH and proximal CTEPH groups

<table>
<thead>
<tr>
<th></th>
<th>IPAH (n=96)</th>
<th>Distal CTEPH (n=35)</th>
<th>Proximal CTEPH (n=68)</th>
<th>p (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemodynamics: mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAP</td>
<td>9.5 (6)</td>
<td>10.2 (7.9)</td>
<td>8.6 (5.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>1.91 (0.68)</td>
<td>2.11 (0.68)</td>
<td>2.07 (0.67)</td>
<td>0.23</td>
</tr>
<tr>
<td>mPAP†</td>
<td>54.8 (13.1)</td>
<td>47.3 (11.9)</td>
<td>45.4 (12.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPR‡</td>
<td>18.1 (8.3)</td>
<td>12.9 (5.2)</td>
<td>12.4 (5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pulmonary function mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ %predicted§</td>
<td>84.0 (16)</td>
<td>74.7 (22.1)</td>
<td>80.4 (18.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>FVC %predicted§</td>
<td>92.0 (16.8)</td>
<td>83.3 (24.7)</td>
<td>95.7 (16.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>TLC %predicted</td>
<td>98.2 (15.2)</td>
<td>90.8 (19.8)</td>
<td>95.6 (15.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>TLCO %predicted</td>
<td></td>
<td></td>
<td>66.3 (19.3)</td>
<td>62.8 (13.4)</td>
</tr>
<tr>
<td>KCO %predicted**</td>
<td>78.8 (22.1)</td>
<td>85.3 (17.4)</td>
<td>91.6 (19.3)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Significant pairwise comparisons are listed below:

* p=0.02 IPAH vs proximal CTEPH
† p<0.001 IPAH vs proximal CTEPH; p=0.008 IPAH vs distal CTEPH
‡ p<0.001 IPAH vs proximal CTEPH; p=0.001 IPAH vs distal CTEPH
§ p=0.007 distal CTEPH vs proximal CTEPH
|| p=0.01 IPAH vs proximal CTEPH; p=0.006 proximal CTEPH vs distal CTEPH
** p=0.002 IPAH vs proximal CTEPH

There were no clinically relevant differences between the groups in terms of either haematological or biochemical results.

**Outcomes**

Follow up data were complete for all subjects, with none lost to follow up.

93.8% of proximal CTEPH subjects improved symptomatically to WHO functional class I or II by the time of their three month post-operative assessment following PEA surgery. During subsequent follow up two subjects died, both of presumed cardiorespiratory causes. Actuarial survival in this highly selected group of proximal CTEPH subjects was 98.5%, 97% and 97% at 1 year, 3 years and 5 years respectively.

A similar proportion of subjects in both distal CTEPH and IPAH groups received targeted therapy (68% vs 66%) during follow up. First-line therapies used included intravenous epoprostenol, intravenous iloprost, subcutaneous treprostinil, nebulised iloprost, bosentan and sildenafil. At 12 months actuarial survival was 86% in IPAH subjects compared with 77% in distal CTEPH. The IPAH group continued to have better survival rates at 3 years after presentation (60% vs. 53%) but survival rates were similar at 5 years (48% vs. 53% for IPAH vs. distal CTEPH). Overall there was no statistically significant difference in survival between these two groups (p=0.68) (Figure 1).

**DISCUSSION**

This study demonstrates that distal and proximal CTEPH patients are comparable in terms of age at presentation, BMPR2 status and prior thromboembolic history, but that they differ from IPAH patients in all these respects. Although all three groups were equally limited in functional terms, IPAH patients had significantly worse haemodynamic parameters at
presentation. Despite these differences, long term survival was similar in both the distal CTEPH and IPAH populations.

There is both histological and clinical evidence to support a role for thrombosis in IPAH(11, 21). Given that other histological features are also common to both CTEPH and IPAH(13), it has been suggested that these two conditions may exist on a continuum of disease. This casts doubt over the presumed embolic origins of CTEPH and would suggest that in situ thrombosis plays a more significant role in the disease. However, if distal CTEPH were to represent an overlap condition, one would expect distal CTEPH patients to share some demographic features with IPAH patients. This study, however, demonstrates that both distal and proximal CTEPH differ from IPAH with respect to key factors such as age and prior thromboembolic history. Moreover, a trend was also seen towards a higher proportion of males in both CTEPH groups compared with IPAH. The age and sex differences between proximal CTEPH and IPAH patients seen here are consistent with previously reported studies, implying that our patient population is comparable to those of other centres(22). The incidence of prior DVT in proximal CTEPH is likewise similar to previously published work(23). The marked difference in DVT incidence between the three groups demonstrated here therefore favours the role of a shared thromboembolic aetiology, common to both distal and proximal CTEPH but not IPAH.

The BMPR2 receptor is a member of the Transforming Growth Factor-β (TGF-β) cell signalling superfamily and plays a critical role in vascular growth, development and maintenance(24). Mutations in the BMPR2 gene underlie the majority of FPAH cases(8), but only a proportion of IPAH cases(9), suggesting that other genetic or environmental factors are also important in sporadic forms of the disease. Although BMPR2 mutations have been described in other forms of pulmonary hypertension(25-27), the prevalence of these mutations in CTEPH has not been specifically studied to date. Although the results of this study are limited by the proportion of DNA samples available, they suggest that BMPR2 mutations are not a feature of either distal or proximal CTEPH. This provides yet further evidence, albeit circumstantial, that the aetiology of both of these forms of CTEPH is distinct from that of IPAH.

Despite the similarities linking distal and proximal CTEPH in this study, there was a significant difference in the prevalence of prior splenectomy between the two groups. Furthermore, splenectomy was also more common in distal CTEPH than in IPAH, albeit not significantly so. Although not new findings, these results confirm previous studies that suggest that splenectomy is more likely to be associated with distal, rather than proximal, disease(20, 22). Splenectomy appears to independently promote a prothrombotic state, possibly through loss of the filtering function of the spleen and consequent persistence of abnormal red cells(15). It is possible that splenectomy is also associated with other abnormalities of haemostasis that may particularly predispose to distal CTEPH. For example, thromboembolic material may be more fragile in these subjects, thus fragmenting more easily within the pulmonary vasculature and triggering more distally distributed disease.

Haemodynamic evaluation is essential for diagnosing pulmonary hypertension, but cannot typically distinguish between the different forms of pulmonary hypertension. In this study, however, there were significant differences between the haemodynamic parameters of the two CTEPH groups and the IPAH group, despite all three groups sharing similar functional characteristics of WHO class and baseline 6MWD. Although this discrepancy between the groups could be attributed to age, virtually all the proximal CTEPH patients returned to WHO functional class I or II following surgery, suggesting that age-related co-morbidities alone were not significantly contributing to exercise limitation. This implies that patients with CTEPH are more functionally limited than their haemodynamic measures suggest. Although PVR is commonly taken as a surrogate of disease severity, another key determinant of right ventricular afterload is pulmonary arterial impedance. This measure of the opposition to
pulsatile (versus mean) components of flow is itself dependent on the mechanical properties of the proximal pulmonary arteries(28). CTEPH affects the more proximal components of the pulmonary vasculature than IPAH, and is thus likely to have a more adverse effect on pulmonary impedance. This would lead to more right ventricular strain, and hence more exercise limitation, than suggested by standard right heart catheterisation measurements alone.

Both restrictive and obstructive spirometric changes have previously been described in IPAH and CTEPH(29-31). Restrictive changes in CTEPH have been attributed to parenchymal scarring resulting from previous pulmonary infarction. This may explain the smaller lung volumes seen in the distal CTEPH group, who had more peripherally distributed disease, compared with the proximal CTEPH group. However, the differences in mean FEV₁, FVC and TLC were small and did not alone allow clear differentiation of the three patient groups. Mean TLCO, however, was also significantly higher in the proximal CTEPH group compared with the other two groups. Following correction for alveolar volume, this difference remained significant between the proximal CTEPH and IPAH groups. TLCO is a function of both pulmonary capillary blood volume (Vc) and pulmonary membrane diffusion capacity (Dm). There is relatively little published data on Vc and Dm in pulmonary hypertension. However, as a large proportion of disease in proximal CTEPH is situated within major vessels, one would expect Dm to be relatively preserved. Moreover, an extensive bronchial collateral circulation often develops in proximal CTEPH which may help maintain Vc, through retrograde perfusion. IPAH patients, conversely, have been shown to have impairment of both Vc and Dm, possibly as a complication of their small vessel vasculopathy(32). As there is proportionally more downstream involvement in distal CTEPH, a reduction in Vc and Dm, similar in magnitude to that of IPAH, would therefore be expected. Although previous work has failed to show a difference in Dm or Vc between CTEPH and IPAH patients, this may have been related to the fact that no differentiation was made between distal and proximal disease(32).

The natural history of a disease is best ascertained by prospectively following a large cohort of untreated patients. However, given the rarity of distal CTEPH, this poses some logistical difficulties, and would require a multicentre approach. Furthermore, there is increasing evidence, albeit from uncontrolled studies, that targeted therapy may be beneficial in these patients, possibly by modifying the IPAH-like vasculopathic changes(33-38). As such, given that there are no licensed treatments for this progressive condition, deteriorating patients are typically managed similarly to IPAH and treated with targeted therapies on a compassionate basis. For these reasons, prospective data on treatment-naïve patients are unlikely to be forthcoming and, historical outcome data must be relied upon in the meantime. When examining outcome in CTEPH, it is important that a clear distinction is made between proximal and distal disease, as management differs so markedly between the two groups. Unfortunately, the two papers that have previously studied outcomes have not made this distinction, and thus there is a paucity of information available regarding distal disease(2, 16). Conversely, outcome in patients with IPAH is much better described(39), such that we have previously been able to validate survival of our own IPAH population against known measures(40). Therefore in this study, using our IPAH population as a benchmark, we were able to assess the relative survival characteristics of distal CTEPH compared with IPAH. The results demonstrate that when both patient groups are managed in a similar manner, outcomes are comparable. This confirms that a diagnosis of distal CTEPH conveys a poor prognosis, leading to almost 50% mortality by three years. As such, there is a clear need for more clinical trials to further define the role of medical therapies in distal CTEPH. Moreover, the more favourable haemodynamic parameters within the distal CTEPH group suggest that standard haemodynamic measures alone may underestimate prognosis in this condition. This may be relevant when considering the timing of referral for transplantation.
An obvious limitation to the study is the small number of subjects present in the distal CTEPH cohort compared with the other two groups, reflecting the relative rarity of the condition. This may have resulted in low power to detect minor or moderate differences between the groups. Another is the wide variation in targeted therapies prescribed to distal CTEPH individuals. The latter reflects the expansion in the number of therapies available for use in this specialty during the period of time studied. This is controlled, to an extent, by the fact that both distal CTEPH patients and IPAH patients are managed alike at our institution and thus receive the most appropriate targeted therapy that is available at the time. A further potential drawback to the study is the diagnosis of distal CTEPH itself. There are no clear universal criteria on what constitutes inoperable disease, and thus the threshold for offering surgery to CTEPH patients may vary from institution to institution. The study was performed in an established PEA centre where almost 300 PEA procedures have been performed. All subjects were assessed with a minimum of two imaging modalities and discussed within a multidisciplinary setting in the presence of experienced specialist surgeons, radiologists and physicians. As such, it is hoped that the distal CTEPH cohort described in this study are representative of patients seen elsewhere. Conversely, the study benefits from being performed within a single centre, thus ensuring a uniform diagnostic approach was taken in all patients. In addition, the proximal CTEPH group examined here was clearly defined by post-operative haemodynamics, thus excluding patients who may have had co-existing proximal and distal disease at presentation.

In summary, this study demonstrates that distal and proximal CTEPH groups share certain demographic features that not only indicate a common aetiology but also help differentiate them from IPAH patients. Despite more favourable haemodynamic measures, distal CTEPH patients experience levels of functional limitation similar to IPAH patients and share an equally poor long term outcome. These results emphasise the importance of securing an early diagnosis in distal CTEPH so that appropriate management can be instituted.

FIGURE LEGENDS
<< Figure 1: Kaplan Meier survival estimates for IPAH and distal CTEPH patient groups >>

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