



Early View

Original article

The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension

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The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension

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Take home message: Outcomes for patients undergoing pulmonary endarterectomy are excellent and superior to patients declining surgery.

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 were 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 percent 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 is registered with clinicaltrials.gov, registration number NCT02565030.

INTRODUCTION

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a potentially curable form of pulmonary hypertension (PH) [1]. It may follow an acute episode of pulmonary embolism (PE) [2, 3] but can present as unexplained PH with no previous history of venous thromboembolism (VTE) [4-6]. 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 [5, 7]. Over the past 20 years the treatment of CTEPH has evolved to include pulmonary endarterectomy (PEA) in operable cases [8] and PH specific therapy for inoperable disease [9-14]. Balloon pulmonary angioplasty is emerging as a potential treatment option in selected patients with inoperable disease [1, 15, 16].

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 [17-19], with 10-year survival of 72-75% [20, 21]. 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 [22, 23]. However, subsequent large registries have shown significant improvements in outcome in a heterogeneous group of non-operated patients [24, 25]. 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 [24, 26]. A significant proportion of patients who have technically operable disease do not undergo surgery for a variety of reasons including comorbidities and patient choice [24-27]. To date, there are only limited data on the clinical course and rationale for treatment decisions in this patient group. In particular there are 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. Some of the results have been previously reported in abstract form [28, 29].

METHODS

Consecutive treatment naïve patients newly diagnosed with CTEPH at the Sheffield Pulmonary Vascular Disease Unit between 1st January 2001 and 30th November 2014 were prospectively recorded in hospital databases. Baseline characteristics, treatment and follow-up data, using a census date of 30th November 2015, were subsequently collected from hospital records and departmental databases. Baseline characteristics, demographics, medical history, pulmonary function, exercise testing, right heart catheter metrics, imaging and treatment were included.

The diagnosis of CTEPH was based on findings obtained after at least 3 months of anticoagulation and required the patient to have undergone right heart catheterisation and to have a mean pulmonary arterial pressure ≥ 25 mmHg 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 [18, 19]. Patients were further classified into CTEPH: a) operated group, b) technically-operable-not-operated group and c) patients with non-surgical disease distribution. The technically operable-not-operated group was further sub-classified into four sub-groups based on the reasons for the surgery not being performed: i) declined surgery (patient choice), ii) being unfit for surgery following multidisciplinary team (MDT) assessment, iii) CTEPH with other contributors to symptoms in addition to clot burden and iv) reason for decision not clear. Suitability for PEA surgery was assessed by a review of clinical and radiological information by the surgical MDT at the national PEA centre, Papworth Hospital.

The date of diagnosis of CTEPH was recorded as the date of the first right heart catheterization. All patients were followed up until death or the census date of 30th November 2015. Ethical approval was granted for this study (REC Reference number 06/Q2308/8).

STATISTICAL ANALYSIS

Descriptive data are presented using mean and standard deviation (SD).

Comparison between groups was made using t-test (for two groups) and ANOVA (with Bonferroni corrections for three groups) for continuous data and Chi-Squared for categorical data. Survival was assessed by the Kaplan-Meier method.

Comparisons between two groups were performed using log-rank test. Prognostic variables were assessed using univariate and multivariate cox regression analysis for survival. Seventy-two variables in CTEPH-surgical-operated and 71 variables in the CTEPH-surgical-not-operated and CTEPH-non-surgical groups were identified based on previous literature [24, 25, 30] and entered into univariate Cox regression analysis. Variables with a p-value of <0.20 at univariate analysis and $<10\%$ missing data were included for the multivariate analysis using the forward logistic regression method. To allow comparison between continuous variables hazard ratios (HR) were scaled using the standard deviation of the variable. A p-value of <0.05 was considered statistically significant. Accuracy of variables for prediction of mortality at 3 years was assessed using receiver operator characteristic (ROC) analysis. Statistical analysis was performed using SPSS software (IBM SPSS statistics version 25) and GraphPad software (Prism).

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 1.

Patient characteristics

CTEPH (whole cohort)

Baseline characteristics for the major groups are summarised in Table 1 and for technically-operable-not-operated subgroups in Table S1. 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 to the census 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 technically operable disease undergoing and not undergoing surgery and those with a non-surgical disease distribution. 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 whilst 0.5% were not anticoagulated. Seventy-six percent of patients received PH 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.

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 1). 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 was commenced at diagnosis and did not lead to delay in referral for surgical consideration or time to surgery (Table S2).

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 all < 0.05 , Table 2).

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 DLco, 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 benefit 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 S1.

CTEPH-non-surgical disease distribution

History of VTE was less common in patients with non-surgical disease. A history of thyroid disease and splenectomy was also a significantly more common in this sub-group compared to patients undergoing PEA (Table 1).

Outcomes

CTEPH (whole cohort)

During a mean follow-up of 4 ± 3 years, 182 (32%) patients died: 51 in the CTEPH-surgical-operated group, 76 in the CTEPH-technically-operable-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-not operated group (87%, 63% and 53%) and CTEPH-non-surgical group (92%, 75% and 59%); $p<0.001$, Figure 2.

CTEPH-operated

Persistent PH (as defined by $mPAP \geq 25$ mmHg) post-PEA surgery was found in 108 (40%) patients in our 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 ($p=0.288$). However, those with a post-operative PVR above the median (3 WU) had a worse prognosis following surgery ($p=0.013$). 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%, $p=0.447$), 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).

CTEPH-declined surgery (patient choice)

The estimated 5-year survival of patients declining surgery was significantly worse than those undergoing PEA (55% versus 83%, $p<0.001$), Figure 3A. The impact of age on long term outcome in patients offered surgery is shown in Figure 3B-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 offered surgery who declined, who had a significantly worse survival than patients with other contributors to symptoms in addition to clot burden ($p < 0.05$), Figure S1.

Prognostic indicators

CTEPH (whole cohort)

Univariate analysis of the whole cohort identified a number of predictors of outcome (Table 3). Independent predictors of mortality identified from multivariate analysis were: pulmonary endarterectomy (HR 0.38, confidence interval (CI) 0.23-0.63), DLco (HR 0.59, CI 0.46-0.74), mixed venous oxygen saturation (SvO₂) (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

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), SvO₂ (HR 0.66, CI 0.49-0.89), DL_{CO} (HR 0.67, CI 0.47-0.95) and the presence of coronary artery disease (HR 2.34, CI 1.11-4.96), Table 4.

CTEPH-declined surgery (patient choice)

Receiver operator curve analysis for prediction of 3-year mortality was performed for the 3 continuous prognostic variables identified at univariate analysis (Table S3): DLco (AUC 0.87), RAP (AUC 0.81) and SvO₂ (AUC 0.85). Using median thresholds of DLco 62%, RAP 11 mmHg, and SvO₂ 62% the sensitivity, specificity, positive predictive and negative predictive values for predicting 3-year mortality were 100%, 63%, 31% and 100%; 80%, 70%, 32% and 95%; and 90%, 60%, 30% and 97%, respectively.

CTEPH-technically operable not operated

For the whole group univariate analysis identified a number of predictors of outcome including age, WHO FC, exercise capacity, pulmonary haemodynamics and comorbidities. Univariate and multivariate analysis for each of the 3 subgroups is shown in Table S3. Independent predictors of outcome were SvO₂ (HR 0.53, CI 0.38-0.76), DLco (HR 0.54, CI 0.38-0.75), and cancer (HR 4.10, CI 2.02-8.37). In those who declined surgery SvO₂ (HR 0.24, CI 0.12-0.51), was an independent predictor of survival, whilst in those unfit for surgery exercise capacity (HR 0.51, CI 0.26-0.96), PVR (HR 1.56, CI 1.02-2.38), and comorbidities (cancer (HR 11.46, CI 3.46-37.99), and CKD (HR 8.87, CI 2.45-32.17)), independently predicted outcome, whilst 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.

DISCUSSION

To our knowledge this is the first study primarily focussing on patients with technically operable CTEPH who did not undergo PEA. Patient 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, DLco 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 [17-19]. Our 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 [24]. 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 [24], Austrian [31, 32] Spanish [25], Italian [33] and Dutch CTEPH registries [34]. Although 482 patients (82%) 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 [24, 34, 35].

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 [22, 23]. 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 SvO₂ and DLco 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 (patient 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 our study [24, 34, 35]. 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 DLco predicted outcome with median thresholds for DLco, right atrial pressure and SvO₂ 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 [36, 37]. 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 patient choice was an independent predictor of a worse outcome. In patients who declined compared to those who underwent surgery, there was a female predominance [27], and gender specific factors related to risk-taking may play a role [38]. 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 peri-operative mortality of <5% and offers the best chance of longer term survival, but requires careful assessment of risks vs benefits for individual patients [21, 24] . We found 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%) [24] but less than the UK (32%) [35] and Dutch (26%) [34] 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) [21, 39] . We noted a female predominance, an increased incidence of thyroid disease and splenectomy and reduced incidence of VTE in this group (Table 1) in keeping with previous reports [33].

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 [24, 32, 35, 40] but in line with waiting times for surgery in the UK during the duration of this study, although UK waiting times are now falling. In keeping with data from the International CTEPH registry, the duration of delay did

not impact on long-term survival [24]. 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 [24]. Importantly, bridging therapy had no effect on time to referral or to surgery. 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 [24]. Importantly, in our study receiving bridging therapy was not associated with adverse outcome at univariate analysis.

Limitations

This study pre-dates 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

To our knowledge we report results from a large consecutively enrolled registry of patients with CTEPH and have been able to compare characteristics and have identified predictors of survival in patients who did not undergo surgery despite having technically operable disease. Our 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.

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Table 1: 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)
DL _{CO} (% 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; SvO₂ = mixed venous oxygen saturation; FEV₁ = forced expiratory volume in one second; DL_{CO} = 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 2: Baseline characteristics of CTEPH-operated group versus patients who declined surgery (patient choice)

	CTEPH-operated	CTEPH declined surgery (patient choice)	p- value
Number	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
DL _{CO} (% 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; SvO₂ = mixed venous oxygen saturation; FEV₁ = forced expiratory volume in one second; DL_{CO} (%) = 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 3: Cox regression survival analysis for CTEPH-whole cohort

		Univariate analysis			Multivariate analysis		
Covariate		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			
DL _{CO} *	/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; SvO₂ = mixed venous oxygen saturation; FEV₁ = forced expiratory volume in one second; DL_{CO} = 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 4: Cox regression survival analysis in CTEPH-technically-operable who were offered surgery (operated group and declined surgery (patient choice) sub-groups)

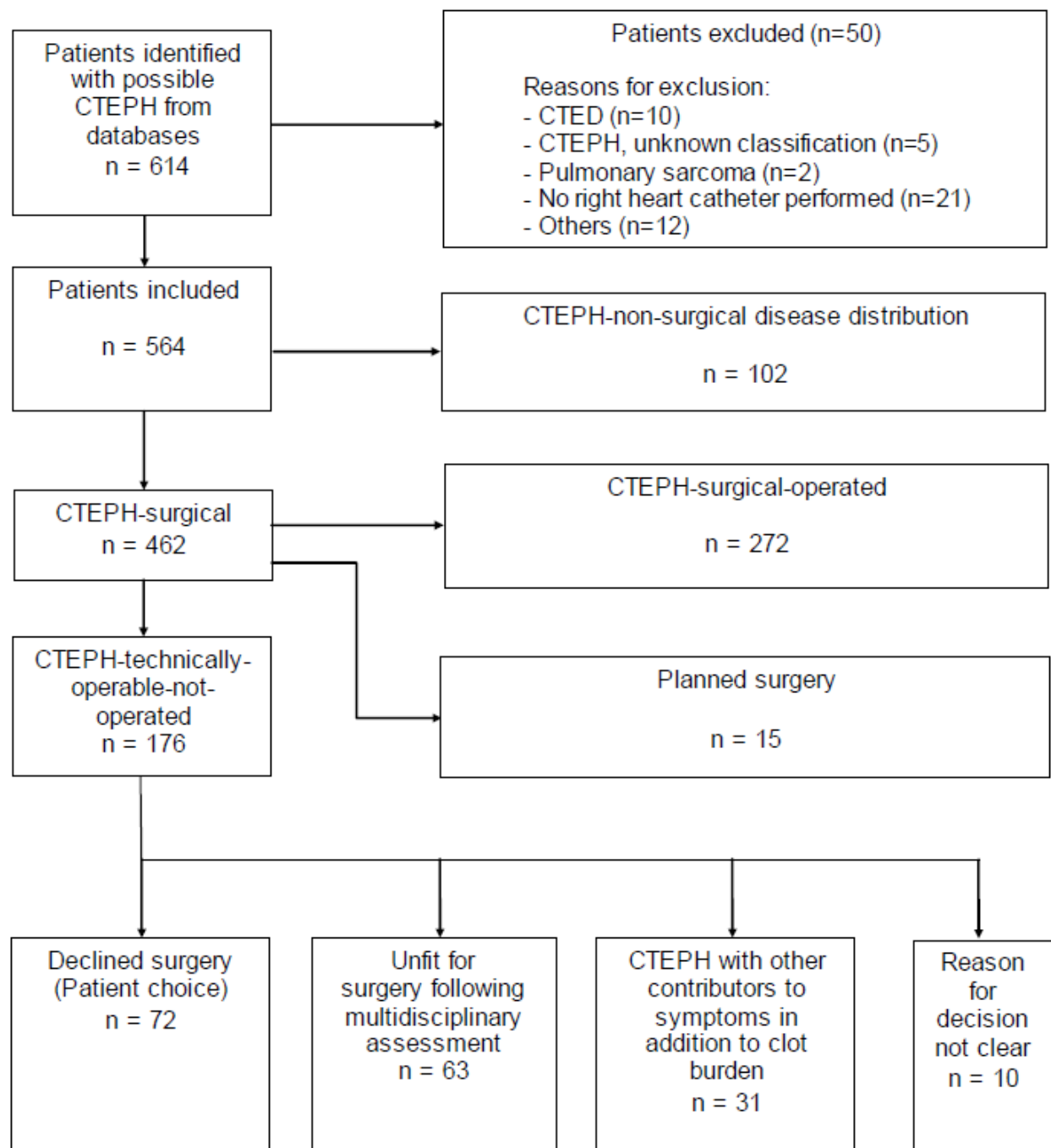
		Univariate analysis			Multivariate analysis		
Covariate		HR	95% CI	p-value	HR	95% CI	p-value
Age*	/15 years	1.71	1.30-2.25	<0.001			
WHO FC	I/II or II/IV ref = I/II	3.98	1.25-12.65	0.019			
Cardiac arrhythmia	ref = absent	2.16	1.03-4.53	0.043			
ISWD*	/185 m	0.56	0.41-0.75	<0.001			
RAP*	/6mmHg	1.57	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
DL _{CO} *	/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; SvO₂ = mixed venous oxygen saturation; FEV₁ = forced expiratory volume in one second; DL_{CO} = 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).

Figure 1: Patient cohort flow chart.



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

Figure 2: Kaplan-Meier estimates of survival from date of diagnosis in CTEPH-operated, CTEPH-technically-operable-not-operated and CTEPH-non-surgical patients.

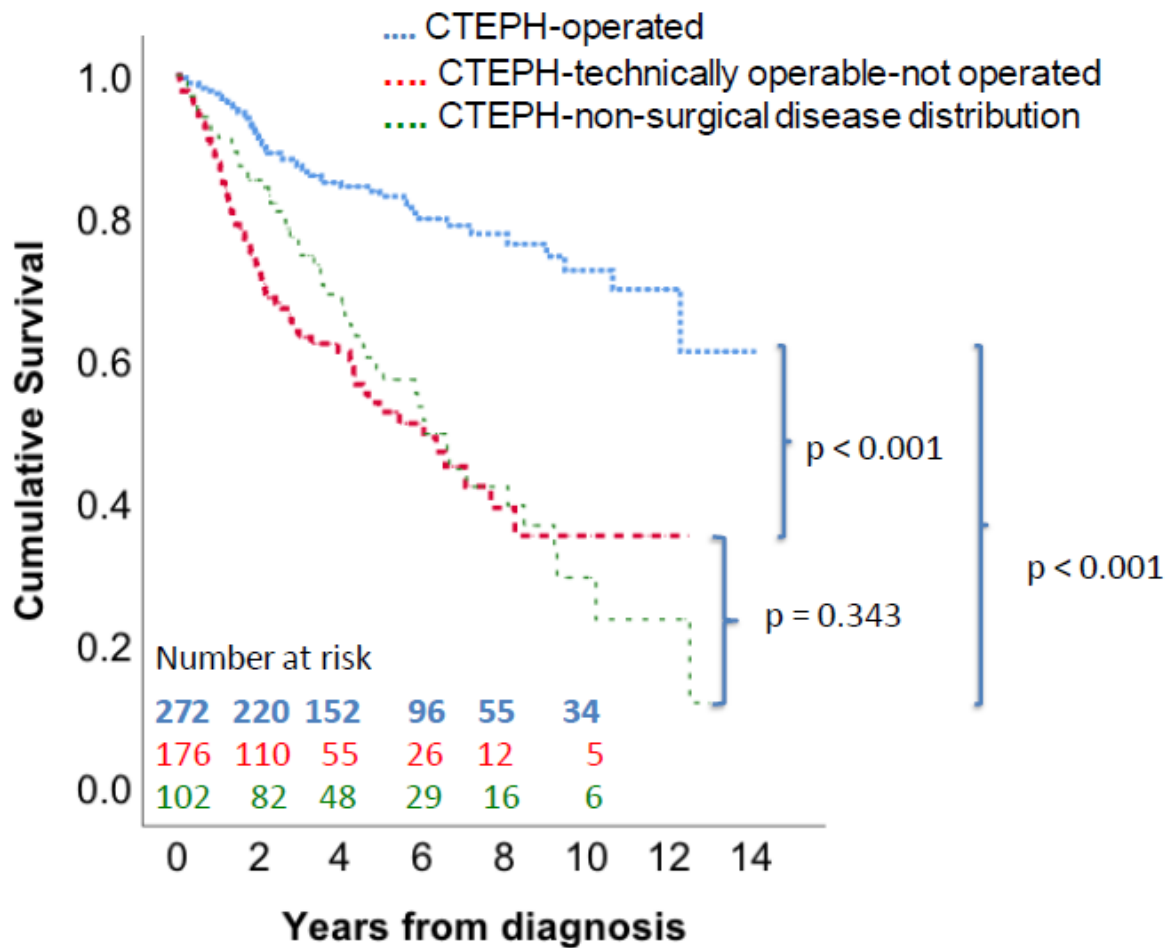
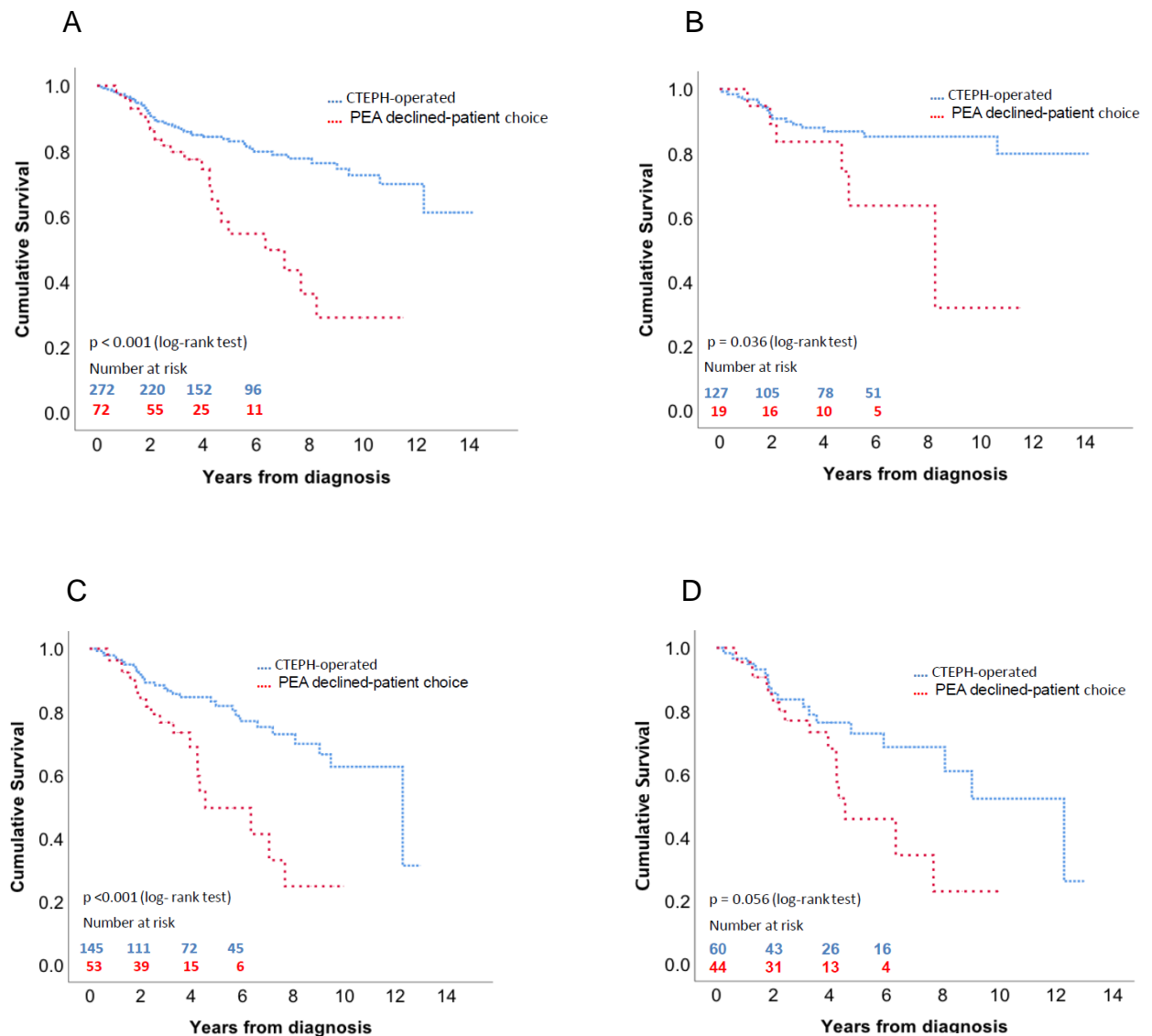


Figure 3: Kaplan-Meier estimates of survival from date of diagnosis comparing outcomes in patients with technically operable CTEPH who were offered surgery and underwent PEA versus patients who declined surgery (patient choice). A: all patients B: patients < 60 yrs, C: patients ≥ 60 years, D: patients ≥70 years



SUPPLEMENTAL TABLES:

Table S1: Baseline characteristics in CTEPH-technically-operable-not-operated subgroups (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	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) [*]
DL _{CO} (% 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; SvO₂ = mixed venous oxygen saturation; FEV₁ = forced expiratory volume in one second; DL_{CO} = 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 S2: 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*	/0.8 L/min/m ²	0.62	0.46-0.82	0.001			
PVR*	/4.6 Wood 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
DL _{CO} *	/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; SvO₂ = mixed venous oxygen saturation; DL_{CO} = 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 S3: 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
DL _{co} *	/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			
DL _{co} *	/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; SvO₂ = mixed venous oxygen saturation; DL_{CO} = 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).

Figure S1: 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.

