Early View

Original article

CAMPBOR score: patient-reported outcomes are improved by pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension (CTEPH)

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Title page

Full Title: CAMPHOR score: patient-reported outcomes are improved by pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension (CTEPH)

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Take-home message:

Patients with CTEPH report significant improvement in patient-reported CAMPHOR scores after pulmonary endarterectomy compared with patients not operated on, but those with clinically significant residual pulmonary hypertension have less benefit.

Journal:

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Abstract

Background

Pulmonary endarterectomy (PEA) is the recommended treatment for eligible patients with chronic thromboembolic pulmonary hypertension (CTEPH). The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) score is an internationally-validated patient-reported outcome (PRO) measure for CTEPH. It assesses 3 domains: activity, quality of life (QoL) and symptoms. We assessed PROs in patients with CTEPH undergoing PEA.

Methods

This retrospective observational study of consecutive CTEPH patients undergoing PEA at the UK national PEA centre between 2006 and 2017 assessed change in CAMPHOR score from baseline (pre-PEA) until up to 5 years post-PEA. CAMPHOR scores were compared between (i) those with and without clinically significant residual PH and (ii) those undergoing PEA and propensity-matched CTEPH patients who were not operated on. The minimally clinically important difference (MCID) was calculated using an anchor-based method.

Results

Of 1324 CTEPH patients who underwent PEA, 1053 (80%) had a CAMPHOR score recorded pre-PEA, 934 (71%) within a year of PEA and 784 (60%) had both. There were significant improvements between pre- and post-PEA in all three CAMPHOR domains (median $\pm$ interquartile range: activity, -5 ± 7 ; QoL, -4 ± 8 ; and symptoms, -7 ± 8 ; $p<0.0001$, all). Improvements in CAMPHOR score were greater and more sustained in those without clinically significant residual PH. CTEPH patients undergoing PEA had better CAMPHOR scores than those not operated on. The MCID in CAMPHOR score was -3 ± 5 for activity, -4 ± 7 for QoL, and -6 ± 7 for symptoms.

Conclusions

PROs are markedly improved by PEA in patients with CTEPH, more so in those without clinically significant residual PH.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is an infrequent but important complication of pulmonary embolism. Organisation and fibrosis of thrombotic material leads to obstruction of proximal pulmonary arteries which, together with a secondary small vessel vasculopathy, results in pulmonary hypertension [1]. CTEPH can lead to debilitating symptoms and functional impairment that affects quality of life (QoL) [2]. CTEPH patients who are eligible for surgery should be offered pulmonary endarterectomy (PEA), which involves removing obstructive thromboembolic material from surgically accessible pulmonary arteries [3]. PEA leads to improved symptoms and better survival in CTEPH [4, 5]. However, up to half of patients will have residual pulmonary hypertension (PH) after PEA that is associated with lower post-operative 6-minute walk distance (6MWD) and worse World Health Organization functional class (WHO FC) [6, 7]. Treatment options for residual PH may include licenced drug therapy or balloon pulmonary angioplasty (BPA) [8-11].

Since 2008, the World Symposium on Pulmonary Hypertension (WSPH) has recommended including patient-reported outcome (PRO) measures as secondary endpoints in clinical PH trials to assess health-related quality of life (HRQoL) [12]. However, PROs remain an underutilised outcome measure in clinical trials despite their relevance to patients [2]. This is partly because changes in PROs have often been more modest than other clinical trial endpoints, such as 6MWD and pulmonary haemodynamics [13-15]. There has also been a reliance on generic PRO measures in PH clinical trials that may lack sensitivity in PH including CTEPH [16].

Several HRQoL measures have been assessed in CTEPH including generic (e.g. 36-Item Short Form Survey (SF-36) [17-19] and EuroQol- 5 Dimension (EQ-5D) [20, 21]) and PH specific scores (EmPHasis-10 [22] and Living with Pulmonary Hypertension questionnaire [LPH] [23]). Disease-specific PROs for PH/CTEPH may be more effective than generic measures in assessing HRQoL and predicting clinical deterioration [13-15]. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) score is the only PRO that was specifically developed in a cohort that included CTEPH and was validated in an adequate sample size [24]. It assesses 3

domains: activity, QoL and symptoms and is an independent predictor of clinical deterioration in CTEPH [14]. The minimally clinical important difference (MCID) is the smallest difference in outcome score that patients perceive as important and has not yet been defined for CAMPHOR [2].

The traditional clinical outcome measures in PH and CTEPH (6MWD, WHO FC, pulmonary haemodynamics and mortality) have several limitations. Survival following PEA has substantially improved, with in-hospital mortality <2.5% in some expert centres, limiting its usage as a future outcome measure [6]. Clinical symptoms may be disproportional to resting pulmonary haemodynamics, which is exemplified by chronic thromboembolic disease with an mPAP < 25mmHg [25]. Finally, functional outcome measures in PH may not correlate with meaningful outcomes such as hospitalisation, initiation of rescue therapy and death [26].

Treatment options for managing CTEPH have broadened to include PEA, BPA, riociguat [3, 8, 11], and medical therapies for pulmonary arterial hypertension (PAH) used off-label [4, 27, 28]. Current and future clinical trials will assess combination treatments particularly for residual PH post-PEA. Therefore, there is an increasing need for robust outcome measures that patients deem important including PROs in CTEPH clinical trials.

The aims of this study were to (i) investigate the change in CAMPHOR score in a large cohort of CTEPH patients undergoing PEA, (ii) determine whether this varies in those with and without clinically significant residual pulmonary hypertension post-PEA, (iii) compare CAMPHOR scores in those undergoing PEA with CTEPH patients not operated on, and (iv) determine the minimally clinically important difference (MCID) for CAMPHOR score in CTEPH.

Methods

Study participants

This retrospective study was approved by the Health Research Authority, UK (IRAS project ID: 238805). Consecutive adult patients with CTEPH who underwent PEA at the national PEA centre (Royal Papworth Hospital, UK) from January 2006 to June 2017 were eligible. Study inclusion/exclusion criteria are summarised in **supplementary figure S1**. CTEPH was diagnosed according to international guidelines [29] and PEA was performed as previously described [5, 29]. Following PEA, patients were reviewed at 6 and 12 months at either Royal Papworth Hospital or their local specialist PH centre and annually thereafter for at least 5 years. Data were prospectively collected using a dedicated PH database. Clinical data (not including survival) and CAMPHOR scores were only available for patients at the time of review at Royal Papworth Hospital, Cambridge, UK.

Patient characteristics at baseline and CAMPHOR score

Baseline data for all patients were recorded at the time of diagnostic right heart catheterisation and pre-operatively for patients with CTEPH undergoing PEA. This included CAMPHOR score, demographics, co-morbidities, pulmonary vasodilator therapy, WHO FC, 6MWD, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and haemodynamics. Operative data included type of surgical disease (Jamieson classification [30]), concomitant surgery, complications and length of stay. Outcome data, including CAMPHOR score, were recorded within 1 year of PEA. The CAMPHOR questionnaire assesses symptoms (25 questions), activity (15 questions) and QoL (25 questions). It takes 8-10 minutes to complete and is negatively weighted with higher scores indicating poorer outcome. Symptoms and QoL are both scored out of 25, and activity out of 30.

Clinically significant residual PH post-PEA

To assess the effect of residual PH on longitudinal CAMPHOR score, patients were dichotomised into those with (mPAP ≥ 30 mmHg) and without (mPAP < 30 mmHg) clinically significant residual PH post-PEA and this threshold has been proposed in previous studies [6, 7]. This relationship was further investigated by stratifying the cohort into subgroups (mPAP post-PEA: < 25 , 25–30, 31–36, 37–42, 43–48 and ≥ 49

mmHg). Additional analyses were performed by stratifying patients by post-PEA PVR (**supplementary materials**).

CAMPHOR score for operated and not-operated CTEPH

CAMPHOR scores from CTEPH patients undergoing PEA were compared with CTEPH patients who were not operated on between 2005 and 2015 at Royal Papworth Hospital. The groups were propensity matched for baseline CAMPHOR score, mPAP, age, sex and year of diagnosis. Matching was performed using the nearest neighbour method and a ratio of 3:1 (PEA:no-PEA).

Minimally clinically important difference

The MCID in CAMPHOR score was calculated using an anchor-based method. Participants were asked to answer an 'anchor' question that assessed their global change in health status since the last review (7-point scale ranging from 'very much better' to 'very much worse') in addition to completing the CAMPHOR questionnaire. The median change in CAMPHOR score from baseline (pre-PEA) to the first follow-up post-PEA was calculated for each point on this scale. The MCID was defined as the median change in CAMPHOR score associated with a "moderately better" health status change. The MCID was confirmed by statistical distribution methods and additionally by utilising the MCID for 6MWD that has previously been defined for PAH (**supplementary materials**) [31]. Sensitivity analyses were performed in different subsets of operated CTEPH patients to confirm that MCIDs were robust (**supplementary materials**).

Survival analysis

Survival from PEA until a census date of April 2018 was recorded using centralised national records. Multivariable Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals (CIs) and associations were confirmed by multiply imputing missing data (**supplementary materials**). Cox models were checked for proportional hazards assumptions, influential observations, non-linearity.

Statistical analyses

Groups were compared using the Mann-Whitney *U* test for continuous data and the Cochran-Armitage test for WHO FC. A false discovery rate adjusted *p*-value was used to account for multiple testing. Data averages are described as median $\pm$ interquartile range (IQR) unless otherwise specified; 95% CIs of the median were calculated using bootstrapping (100 replicates) and the percentile method. Change from baseline (pre-PEA) were calculated as the median of differences. Pearson correlation coefficient described associations between complete pairs of outcomes or CTEPH severity variables including CAMPHOR score. Variables associated with CAMPHOR were assessed using multivariable linear models. Multiple imputation was used for a sensitivity analysis of longitudinal CAMPHOR scores to assess for bias in the complete cases analysis.

Results

In total, 1324 patients with CTEPH underwent PEA and were included in the main analysis. The cohort characteristics are summarised in **table 1**. Of these patients, 1053 (80%) had a CAMPHOR score recorded at baseline (pre-PEA), 934 (71%) at follow-up within a year of PEA and 784 (60%) had scores at both time points. The median $\pm$ IQR time to follow-up CAMPHOR score was 139 ± 79 days.

Median $\pm$ IQR change from baseline (pre-PEA) to post-PEA follow-up (within 1 year) for the three CAMPHOR sub-scores indicated a significant improvement in all three domains: activity, -5 ± 7 ; QoL, -4 ± 8 ; and symptoms, -7 ± 8 ($p < 0.0001$, all; **table 2**). There were also significant improvements in 6MWD, NT-proBNP, WHO FC and haemodynamics ($p < 0.0001$, all; **table 2**). The improvements in CAMPHOR score were sustained for 5 years post-PEA (**figure 1**, **supplementary table S1**). To investigate potential confounding from CTEPH patients with missing pre- and post-PEA CAMPHOR scores, multiple imputation was performed. As the change in CAMPHOR score from baseline in the multiply imputed analysis was consistent with the complete cases analysis there was no significant bias from missingness (**supplementary table S2**).

Clinically significant residual PH post-PEA

Patients were dichotomised into those with (n=369), and those without (n=685) clinically significant residual PH post-PEA. Patient characteristics in these groups are summarised in **supplementary table S3**. There were significant post-operative improvements in CAMPHOR compared with baseline in the no residual PH group (median $\pm$ IQR change from baseline: activity, -5 ± 7 ; QoL, -5 ± 9 ; symptoms, -8 ± 8 ; $p < 0.0001$, all) and residual PH group (activity, -4 ± 6 ; QoL, -3 ± 6 ; symptoms, -6 ± 7 ; $p < 0.0001$, all). Patients with no residual PH had greater improvements than those with residual PH (**figure 2a**). Furthermore, the improvements in the no residual PH group were better sustained over 5 years than in those with residual PH, who experienced a worsening trend in CAMPHOR score 2–3 years after PEA (**figure 2a**). When patients were stratified by mPAP or PVR post-PEA, there was a worsening of CAMPHOR scores as mPAP or PVR increased (**figure 2b**; **supplementary figure S2**).

CAMPHOR score for operated and not-operated CTEPH

There were 198 patients with CTEPH not operated on at Royal Papworth Hospital during 2005–2015. As the PEA and no-PEA CTEPH groups differed in baseline variables, including CAMPHOR score (**supplementary table S4**), propensity matching was performed. This resulted in 132 patients not operated on (no-PEA) matched to 396 patients who underwent PEA. The not operated group was heterogeneous and the reasons for not undergoing PEA included: distal, surgically inaccessible disease (n=56), comorbidities (n=31), patient declined the operation (n=19) and other reasons (n=26), including a combination of these factors or limited disease/symptoms. The characteristics of the two groups following propensity matching are summarised in **supplementary table S5**. CAMPHOR scores at follow-up years 1 and 2 were significantly worse in the no-PEA group than in the PEA group ($p<0.0001$, all domains) (**figure 3**; **supplementary table S5**).

CAMPHOR correlation and association

There was a moderate negative correlation between the change from baseline to 1-year post-PEA in CAMPHOR activity score and 6MWD (Pearson correlation coefficient, -0.4 ; **supplementary figure S3**). Correlations between the change from baseline to 1 year post-PEA in CAMPHOR score and changes in both WHO FC and haemodynamic parameters were relatively weak. A multivariable linear regression analysis of CAMPHOR domain scores at baseline demonstrated that pre-PEA CAMPHOR score (activity, QoL and symptoms) was associated with age, and the CAMPHOR activity domain was associated with 6MWD, but there was no association with haemodynamics (**supplementary table S6**).

Minimally clinically important difference

The MCID in CAMPHOR scores associated with a moderately better health status change following PEA were: activity (median $\pm$ IQR), -3 ± 5 ; QoL, -4 ± 7 ; and symptoms, -6 ± 7 (**table 3**). Importantly, the median change in CAMPHOR score from baseline (pre-PEA) to post-PEA follow-up within a year (described above; **figure 1** and **supplementary table S1**) exceeded these MCID thresholds. The MCIDs were consistent across different subgroups in the sensitivity analyses (**supplementary materials**). The changes in CAMPHOR score at 1 year post PEA

among patients with residual PH (described above; **figure 2** and **supplementary table S2**) exceeded or equalled the MCID threshold for activity and symptoms but not QoL.

Survival

Age was the only variable at baseline (pre-PEA) that was significantly associated with 1 year survival post-PEA (hazard ratio [95% CI], 1.17 (1.02-1.35) per 5-year age increase ($p=0.0288$) (**table 4**). The 3 domains of the CAMPHOR score at baseline were not associated with 1 year survival following PEA. The same findings occurred when multiply imputed data were considered with the exception of a nominal association for sex (**supplementary table S7**). Additional survival analyses to investigate if CTEPH patients with greater CAMPHOR improvement post-PEA also had improved long-term survival is presented in the **supplementary materials**.

Discussion

This is the largest study to date of PROs in patients with CTEPH and in patients undergoing PEA. There were significant improvements in the CAMPHOR domains of activity, QoL and symptoms following PEA, and importantly these were sustained for up to 5 years. CTEPH patients with no clinically significant residual PH (mPAP < 30mmHg) had greater improvements in CAMPHOR compared to those with residual PH. CAMPHOR scores were also better in patients who had undergone PEA compared with those who were not operated on. The MCID in each domain of the CAMPHOR score was established as activity -3, QoL -4 and symptoms -6 points.

In contrast to previous findings [32], correlations between CAMPHOR scores and other clinical outcomes (WHO FC, pulmonary haemodynamics) were relatively weak. The only moderate correlation was between an improvement in CAMPHOR activity score and 6MWD. This suggests that improved physiological and functional outcome measures may not translate into improvements deemed important to patients such as QoL. Therefore, the CAMPHOR score provides important additional utility to assessing outcomes for CTEPH patients undergoing PEA.

Previous studies have reported improved PROs following PEA however, they have been limited by reliance on generic PROs, small sample sizes or absence of MCIDs for the PRO tool [18, 33-35]. An advantage of the CAMPHOR score over generic and PH-specific PROs is its development and validation in CTEPH with multiple domains that are specific to CTPEH patients. The present study, in a large cohort of CTEPH patients undergoing PEA demonstrated an improvement in CAMPHOR score that exceeded the defined MCID and was sustained for up to 5 years. Patients with clinically significant PH following PEA had CAMPHOR activity and symptom improvements greater than the MCID. This is consistent with previous smaller studies using generic PROs [18, 34]. However, in the residual PH group the QoL change did not quite exceed the MCID threshold and improvements over 5 years were less sustained. As the improvements in CAMPHOR score following PEA were lower in patients with residual PH, additional treatment modalities including BPA and licenced pulmonary artery vasodilators need consideration in this group [10, 36]. Furthermore, as there was a graduation of worsening CAMPHOR scores with

increasing post-PEA mPAP and PVR, additional treatment modalities following PEA may benefit from a stratified approach.

We have previously reported improved CAMPHOR score in a cohort of CTED patients undergoing PEA and these improvements would exceed the MCID defined in the present study [25]. This confirms that in selected CTED patients, PEA offers significant improvements in PROs including QoL, which is a more meaningful outcome than some traditional measures including haemodynamics. PROs such as CAMPHOR score should be utilised more widely in future studies of CTEPH as recommended by the WSPH [37]. This is particularly relevant in scenarios where more modest improvements in functional, haemodynamic and survival outcome measures are expected, including residual PH post-PEA, CTED and clinical trials of additive and combination therapies in CTEPH.

Patients with CTEPH undergoing PEA had better longitudinal CAMPHOR scores than a propensity matched group of not operated patients. This is consistent with a recent study in CTEPH that reported improved survival in patients undergoing PEA compared to those with operable disease but declining PEA surgery [38]. Our CAMPHOR data further substantiates that PEA is the guideline recommended treatment for patients with CTEPH as it results in improved PROs in addition to the known improved functional, haemodynamic and survival outcomes [4, 5].

This study has a number of strengths including the large sample size, prospective data collection of consecutive patients using a dedicated PH database and is the first study to establish the MCID for the CAMPHOR score in CTEPH. Whilst patients were referred by a number of specialist PH centres, one limitation is that the majority of data included in the study was from a single national PEA centre. This contributed to incomplete longitudinal data for the CAMPHOR score and a different number of patients at each timepoint. This was addressed by multiple imputation that produced results similar to complete case analyses. Another limitation is that the not operated CTEPH group were heterogenous in the reasons that PEA was not undertaken, and the analysis in this group should be considered exploratory. The MCIDs were defined for operated CTEPH patients and may not apply to the not-operated CTEPH cohort. Finally, there was incomplete data on follow-up medications, which limited

an assessment of the effect of pulmonary vasodilator therapy on CAMPHOR score in the operated and not-operated groups.

In conclusion, PROs are markedly improved by PEA in patients with CTEPH, more so in those without clinically significant residual PH or those not operated on. The MCID was established for CTEPH, and PEA resulted in improvements greater than this threshold. This provides a benchmark against which future therapeutic interventions can be assessed and PROs should be utilised more widely in future CTEPH studies.

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Tables

TABLE 1

Patient demographics and characteristics at baseline (n=1324)

	n	CTEPH PEA
Age at PEA, years	1324	61 ± 21
Women, n (%)	1324	619 (46.8)
Year of PEA	1324	2013 ± 5
Comorbidities, n (%)		
Atrial fibrillation/flutter	1079	98 (9.1)
COPD	1144	81 (7.1)
Diabetes	1146	99 (8.6)
Systemic hypertension	873	326 (37.3)
Ischaemic heart disease	1142	134 (11.7)
Malignancy	1077	113 (10.5)
Pulmonary vasodilator medication, n (%)	1184	346 (29)
CAMPBOR score		
Activity	1053	11 ± 9
Quality of life	1053	11 ± 11
Symptoms	1053	13 ± 10
WHO FC, n (%)	1265	
1		0 (0)
2		161 (12.7)
3		997 (77.8)
4		107 (8.5)
6MWD, metres	1117	297 ± 190
NT-proBNP, pg/mL	448	660 ± 1796
Haemodynamics		
mPAP, mmHg	1225	45 ± 15
CI, L/min/m ²	1171	2.14 ± 0.79
PVR, WU	1192	8.49 ± 6.01
RAP, mmHg	744	9 ± 8
PCWP, mmHg	933	11 ± 5
Type of surgical disease^a, n (%)	1225	

1		184 (15)
2		720 (58.8)
3		319 (26)
4		2 (0.2)
Cardiac bypass time , minutes	1136	321 ± 67
Arrest time^b , minutes	999	37 ± 15.5
Concomitant surgery , n (%)	1299	
ASD / PFO closure		44 (3.4)
AVR		13 (1)
CABG		95 (7.3)
MVR		12 (0.9)
Complications , n (%)		
Renal replacement therapy	1025	57 (5.6)
ECMO	1158	64 (5.5)
Pneumonia	1102	138 (12.5)
Re-intubation	1114	104 (9.3)
Return to theatre	1096	84 (7.7)
Tracheostomy	1109	67 (6)
Length of stay , days		
Intensive care unit	1075	4 ± 3
Total hospital	1196	14.5 ± 10
In-hospital mortality , n (%)	1313	49 (3.7)

Data are median ± IQR unless stated otherwise. Data were recorded closest to the time of diagnosis and pre-PEA for 6MWD, NT-proBNP, pulmonary haemodynamics, WHO FC, CAMPHOR score and pulmonary vasodilator medication. N=1324 total cohort.

6MWD: 6-minute walk distance; AVR: aortic valve replacement; CABG: coronary artery bypass graft; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review score; CI: cardiac index; ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; mPAP: mean pulmonary arterial pressure; MVR: mitral valve replacement; PFO/ASD: patent foramen ovale / atrial septal defect; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP:

right atrial pressure; WHO FC: World Health Organization functional class; WU: Wood units.

^aJamieson classification – intraoperative surgical disease classification preceding the 6th World Pulmonary Hypertension Symposium update [30].

^barrest time refers to deep hypothermic circulatory arrest.

TABLE 2

Outcome measures pre-PEA, post-PEA and change from baseline in patients with CTEPH

Outcome	n	Pre-PEA (baseline)	Post-PEA (follow-up within 1 year)	Change from baseline	<i>P</i> value
CAMPBOR score					
Activity	784	11 ± 9 (11,12)	6 ± 9 (5,6)	-5 ± 7 (-5, -4)	<0.0001
QoL	784	11 ± 11 (10,12)	3 ± 10 (3, 4)	-4 ± 8 (-5, -4)	<0.0001
Symptoms	784	13 ± 10 (12,14)	4 ± 7 (3,4)	-7 ± 8 (-8, -7)	<0.0001
6MWD , metres	676	309 ± 170 (300, 320)	366 ± 159 (356, 380)	50 ± 109 (40, 56)	<0.0001
NT-proBNP , pg/mL	326	678 ± 1832 (491, 783)	227 ± 411 (182, 260)	-210 ± 1358 (-398, -98)	<0.0001
WHO FC , n (%)	1058				<0.0001
1		0 (0%)	291 (28%)	—	
2		134 (13%)	473 (45%)	—	
3		822 (79%)	272 (26%)	—	
4		90 (9%)	10 (1%)	—	
Haemodynamics					
CI, L/min/m ²	949	2.17 ± 0.76 (2.1, 2.2)	2.3 ± 0.68 (2.26, 2.34)	0.14 ± 0.87(0.1, 0.19)	<0.0001
mPAP, mmHg	994	45 ± 15 (45, 46)	25 ± 13 (24, 26)	-17 ± 17 (-18, -16)	<0.0001
PVR, WU	963	8.36 ± 5.93 (7.91, 8.79)	3.18 ± 2.8 (3.01, 3.29)	-4.29 ± 5.71 (-4.69, -3.94)	<0.0001
RAP, mmHg	624	9 ± 7 (9, 10)	7 ± 4 (6, 7)	-2 ± 7 (-3, -2)	<0.0001
PCWP, mmHg	677	11 ± 5 (11, 12)	10 ± 5 (10, 11)	-1 ± 6 (-1, 0)	<0.0001

Data are median $\pm$ IQR (95% CI) or n (%) unless otherwise stated. n is the number of individuals with results *both* pre- and post-PEA from an overall cohort of n=1324. *P*-values were adjusted by false-discovery rate and calculated using the Mann-Whitney *U* test for continuous data and the Cochran-Armitage test for WHO FC. Change from baseline is the median of differences.

6MWD: 6-minute walk distance; CI: cardiac index; CTEPH: chronic thromboembolic pulmonary hypertension; IQR: interquartile range; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCWP: pulmonary capillary wedge pressure; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WHO FC: World Health Organization Functional Class; WU: Wood units.

TABLE 3

Minimally clinically important difference in CAMPHOR score for patients with CTEPH undergoing PEA

Health status change	n	CAMPHOR domain		
		Activity	QoL	Symptoms
Very much better	336	-6 ± 8 (-6, -5)	-5 ± 8 (-6, -5)	-8 ± 8 (-9, -8)
Moderately better	158	-3 ± 5 (-4, -2)	-4 ± 7 (-5, -3)	-6 ± 7 (-7, -6)
A little better	90	-3 ± 4 (-4, -2)	-2 ± 6 (-3, -1)	-5 ± 8 (-6, -3)
Not changed	34	-2 ± 6 (-4, 0)	-1 ± 4 (-2, 0)	-2 ± 6 (-5, 0)
A little worse	20	1 ± 6 (-1, 3)	2 ± 8 (-7, 0)	-2 ± 5 (-3, 2)
Moderately worse	13	1 ± 6 (-3, 3)	-1 ± 4 (-4, 0)	0 ± 5 (-3, 2)
Very much worse	4	-4 ± 20 (-14, 19)	1 ± 12 (-6, 15)	-3 ± 7 (-13, 11)

Data are median ± IQR (95% CI). The change from baseline (pre-PEA) in CAMPHOR score at 1 year post PEA, in relation to ratings to a global health status change question. A “moderately better” change in health status was used to define the MCID. Of 784 with a change from baseline CAMPHOR score, 655 (84%) also had a global health status change recorded and were included in the MCID analysis. A very limited number of patients had worse global health status changes (“A little worse”, “Moderately worse” or “Very much worse”) following PEA resulting in large confidence intervals. CI: confidence interval; IQR: interquartile range; QoL: quality of life.

TABLE 4

Cox proportional hazards model of baseline variables and survival 1 year post-PEA in CTEPH using complete cases

	Unit change	HR	95% CI	<i>P</i> value
CAMPHOR				
Activity	1 point	1.03	0.95, 1.11	0.493
QoL	1 point	1.05	0.96, 1.14	0.272
Symptoms	1 point	0.96	0.88, 1.05	0.400
Age	5 years	1.17	1.02, 1.35	0.0288
Sex: Male		0.53	0.27, 1.04	0.0632
6MWD	10 metres	0.97	0.94, 1.00	0.0867
Haemodynamics				
Cardiac index	0.1 L/min/m ²	0.98	0.90, 1.06	0.564
mPAP	5 mmHg	0.97	0.78, 1.2	0.769
PVR	1 WU	1.03	0.92, 1.15	0.603

The association between baseline, pre-PEA variables and 1 year survival following PEA was assessed. CAMPHOR score, 6MWD and haemodynamics are baseline, pre-PEA. Complete cases data was used for this cox proportional hazard model, which included 657 individuals and 38 deaths (667 observations were removed due to incomplete data). 6MWD: 6-minute walk distance; CI: confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; HR: hazard ratio; mPAP: mean pulmonary arterial pressure; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; QoL: quality of life; WU: Wood units.

Figures

FIGURE 1

Longitudinal summary of median CAMPHOR scores among patients with CTEPH undergoing PEA. Data are median score and 95% CI at each time point. The y-axis is truncated at 20 to improve visualisation (maximum scores: activity = 30, QoL and Symptoms = 25). P-values are calculated with respect to baseline values. **** $p \leq 0.0001$. The number of individuals and summary data for each timepoint are summarised in **supplementary table S1**. CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy.

FIGURE 2

a) Groups were dichotomised by those with (n=369) and without (n=685) clinically significant residual PH (≥ 30 mmHg) assessed by right heart catheterisation within 1 year of PEA. Data are median (95% CI) at each time point. P-values compare residual PH post-PEA and no residual PH post-PEA at each time point using the Mann-Whitney U test. The number of individuals and summary data for each timepoint are summarised in **supplementary table S3**. b) Groups were subdivided by post-PEA mPAP groups: <25 (n=410), 25-30 (n=181), 31-36 (n=120), 37-42 (n=78), 43-48 (n=43), >49 (n=33). The median score is plotted at each time point. 95% CIs are not displayed to improve visualisation.

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; **** $p \leq 0.0001$. CI: confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy; PH: pulmonary hypertension.

FIGURE 3

CAMPHOR score over time among propensity-matched individuals with CTEPH that underwent (n=396) and did not undergo (n=132) PEA. Groups were propensity matched (3:1) by baseline CAMPHOR score, mPAP, age, sex and year of diagnosis. The median score and 95% CI are plotted at each time point. *P*-values are calculated between PEA and no-PEA groups at each time point using the Mann-Whitney *U* test. The number of individuals and summary data for each timepoint are summarised in **supplementary table S5**. CI: confidence interval; mPAP: mean pulmonary arterial pressure; PEA: post-pulmonary endarterectomy; PH: pulmonary hypertension.

SUPPLEMENTARY MATERIAL

Supplementary methods

Study participants

Follow-up clinical data and CAMPHOR scores were only available for patients reviewed at Royal Papworth Hospital. Survival data was available for the whole study cohort.

Landmark analysis

To assess potential bias in the time from PEA surgery and CAMPHOR change from baseline, a landmark analysis was performed. Individuals that had a follow-up CAMPHOR score at least 9 months post-PEA were included in the analysis (n=588). The first available CAMPHOR score after 9 months was used to calculate the change from baseline (pre-PEA).

Post-PEA PVR

The effect of post-PEA pulmonary vascular resistance (PVR) on longitudinal CAMPHOR score was investigated. CTEPH patients were subdivided by post-PEA PVR into the following groups: < 3 Wood units (WU) (n=400), 3-5 WU (n=260), > 5-7 WU (n=102). > 7 WU (n=104). The median CAMPHOR score was calculated at each timepoint for each PVR group up to 5 years post-PEA.

Minimally clinically important difference

The MCID in CAMPHOR score was calculated using statistical distribution-based methods. This included calculating 0.5 standard deviations for each CAMPHOR domain of the change from baseline (the difference between pre-PEA and post-PEA within 1 year scores) [1]. The MCID was also calculated using the effect size by dividing the change from baseline CAMPHOR score by 0.2 standard deviations of the baseline CAMPHOR scores [1].

The MCID in CAMPHOR score was also calculated with reference to the 6MWD MCID for pulmonary arterial hypertension (PAH). The MCID for PAH has previously been reported as approximately 33m (range 25.1 – 38.6m) [2]. The change in CAMPHOR score from baseline in CTEPH patients that had a 6MWD change from baseline of between 25.1 and 38.6m represented the CAMPHOR MCID with this method.

Sensitivity analyses

Sensitivity analyses were performed to assess for subgroups that may be confounding the MCID estimates. CAMPHOR MCID calculations were repeated in subgroups using the global change in health status anchor method, with “moderately better” representing the MCID. The sensitivity analysis subgroups included: a “no concurrent surgery” group that did not have additional surgery procedures (e.g. ASD/PFO closure, AVR, CABG or MVR) during the PEA operation, a “no cancer” group *without* a comorbidity of cancer recorded and PVR groups that were stratified by PVR at baseline pre-PEA.

MCID responder analysis

The differences in CTEPH patients that were above and below the defined CAMPHOR MCIDs were investigated. Individuals were dichotomised into those above (“responders”; more negative CAMPHOR) and below the activity (-3), QoL (-4) and symptoms (-6) MCIDs. The following patient characteristics were recorded at baseline (pre-PEA) and where applicable, follow-up within a year of PEA: age, sex, year of PEA, CAMPHOR score, WHO FC, 6MWD, NT-proBNP, haemodynamics, type of surgical disease, cardiac bypass time, arrest time and length of stay.

Survival analysis

An exploratory analysis of the effect of pulmonary capillary wedge pressure (PCWP) on 1 year survival post-PEA was assessed by constructing a Cox proportional hazards model using the same methodology and variables as presented in **table 4**, with the addition of the variable PCWP. PCWP was not used in the main **table 4** model due to the variable missingness and consequent loss of power.

Additional survival analyses were performed to establish if CTEPH patients with greater CAMPHOR improvement post-PEA also had improved long-term survival. Post-PEA long term survival differences between groups with different CAMPHOR change from baseline were assessed using Kaplan-Meier plots. Groups were determined by dividing the CAMPHOR change from baseline (pre- to follow-up within 1 year post-PEA) into tertiles. CTEPH patients in the highest tertile had the greatest improvement in CAMPHOR score. Survival was investigated from the first follow-up CAMPHOR score (post-PEA) for up to 5 years. The log-rank test was used to assess statistical differences between tertile groups.

Statistical analysis

Missing data were multiply imputed with chained equations (100 imputations and 5 iterations) using the MICE R package [3]. Data was assumed to be missing at random after analysis of missingness patterns. Imputed variables were: CAMPHOR score, 6MWD, WHO functional class, haemodynamics (cardiac index, mPAP, pulmonary vascular resistance [PVR]), cumulative hazard and survival status. The predictor matrix also included age, sex, referral centre, year of PEA and surgical disease type. Variable distributions, correlations, missingness patterns and influx-outflux plots were assessed prior to multiple imputation. Predictive mean matching was used for continuous variables, polytomous logistic regression for WHO functional class and logistic regression for survival status. Imputation quality was assessed by visualizing diagnostic plots. Estimates from Cox proportional hazards models were pooled using Rubin's rules in the MICE R package and the psfmi R package [4, 5]. The cox models were checked for proportional hazards assumptions, influential observations and non-linearity. Both the results of the multiply imputed Cox proportional hazards models and complete cases analysis are presented. Multiple imputation was also used as a sensitivity analysis of longitudinal CAMPHOR scores to assess for bias in the complete cases analysis.

Multivariable linear models were checked for normality of residuals, homoscedasticity and multicollinearity.

Software

The analysis was performed in R v3.5.1 [6] and RStudio v1.1.463 [7] using the following packages: modelr (bootstrapping) [8], tidyverse and purrr (data wrangling) [9, 10], coin (Cochran-Armitage test) [11], survival (Cox proportional hazards models) [12], MatchIt (propensity matching) [13], ggcorrplot (correlation matrix), mice (multiple imputation) [3], psfmi (pooling imputed Cox proportional hazards models) [5].

Supplementary results

Landmark analysis

The median time to follow-up CAMPHOR score was 375 ± 57 days for the 9-month post-PEA landmark analysis. The median $\pm$ IQR change from baseline in the three CAMPHOR domains were: activity, -5 ± 7 ; QoL, -5 ± 9 ; and symptoms, -7 ± 7 (**supplementary table S8**). This is very similar to the CAMPHOR change from baseline in the main analysis ($n=784$; non-landmark analysis): activity, -5 ± 7 ; QoL, -4 ± 8 ; and symptoms, -7 ± 8 .

Post-PEA PVR

CTEPH patients with higher post-PEA PVR had less improvement in CAMPHOR scores (**supplementary figure S2**). Those with a post-PEA PVR < 3 WU had a marked improvement in CAMPHOR score that was sustained for up to 5 years.

Minimally clinically important difference

The MCID in the 3 CAMPHOR domains were: activity -3, QoL -3 and symptoms -3 when using 0.5 standard deviations to define the MCID. This compares with activity -3, QoL -4 and symptoms -6 when using an anchor-based method. Activity and QoL are similar with both methods whereas the MCID are lower for symptoms using a distribution-based method. Using effect size, the MCID for each of the 3 CAMPHOR domains were: activity -4, QoL -4 and symptoms -6, which is similar to the anchor-based MCIDs.

Using the MCID for the 6MWD from previous PAH studies, the MCID in the 3 CAMPHOR domains were: activity (median $\pm$ IQR), -5 ± 5 ; QoL, -3 ± 10 ; and symptoms, -7 ± 10 (**supplementary table S9**). This is similar to the MCID estimates reported in **table 3** using a global health change anchor. The activity MCID appears lower (-5 versus -3 using a global health change anchor) however, the 95% confidence intervals are wider (-6 , -3) and they include the CAMPHOR activity MCID calculated using the global health change anchor method.

The CAMPHOR MCID utilising a global health change anchor, statistical distribution methods and with reference to the 6MWD MCID for PAH all produce similar results. We have chosen to report the anchor-based method as it relates to a global change in health status that relates to a patient experience, is the most suitable metric across the heterogeneous domains of the CAMPHOR score and its calculation utilises a larger group than the 6MWD method, producing more robust estimates with narrower confidence intervals.

Sensitivity analyses

In the “no concurrent surgery” group the CAMPHOR MCIDs were: activity, -3 ± 5 ; QoL, -5 ± 8 ; and symptoms -7 ± 8 (**supplementary table S10**). In the “no cancer” group the CAMPHOR MCIDs were: activity, -3 ± 5 ; QoL, -4 ± 8 ; and symptoms -6 ± 7 . These sensitivity analyses are similar to the main CAMPHOR MCID estimates of activity -3, QoL -4 and symptoms -6 (**table 3**).

The median CAMPHOR MCIDs in the post-PEA PVR groups varied across groups (**supplementary table S10**). A limited number of patients were included in this analysis (n: < 3 WU = 66; 3-5 WU = 44; 5-7 WU = 16; >7 WU = 15) resulting in wide confidence intervals. Whilst the confidence intervals for all PVR groups included the main MCID estimates (activity -3, QoL -4 and symptoms -6), this analysis should be considered exploratory and underpowered.

MCID responder analysis

Of 784 patients with both pre- and post-PEA CAMPHOR scores, there were 527 (67%) above the activity MCID (“responders”), 437 (56%) above the QoL MCID and 481 (61%) above the symptoms MCID.

Responders (activity, QoL and symptoms) have a greater improvement in WHO FC, 6MWD, NT-proBNP and have more severe pre-PEA haemodynamics but greater improvement post-PEA than non-responders (**supplementary tables S11-13**). Responders have higher starting CAMPHOR scores and a greater improvement than non-responders, although this is also related to the way the groups were dichotomised by CAMPHOR score MCID.

Survival analysis

Baseline PCWP was not associated with 1 year post-PEA survival using a Cox proportional hazards model of complete cases, and its inclusion had very minimal effect on the hazard ratios and associations presented in **table 4 (supplementary table S14)**.

There was no difference in long-term post-PEA survival between different activity and symptom (change from baseline) tertiles ($p = 0.1$, both) (**supplementary figures S4 and S6**). There was a significant difference in QoL tertiles ($p=0.01$), with CTEPH in the highest tertile having better long-term survival (**supplementary figure S5**). However, no domain of the CAMPHOR score (change from baseline) was associated with long-term survival when adjusted for age, sex, change in 6MWD and change in haemodynamics in a Cox proportional hazards model (**supplementary table S15**). In the same model, age was the only variable associated with long-term post-PEA survival in a complete cases analysis and additionally change in mPAP and sex in a multiply imputed analysis (**supplementary table S15**).

FIGURE S1

Flow chart of study design. CTEPH, Chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy. Non-CTEPH patients included those with chronic thromboembolic disease (without pulmonary hypertension) and pulmonary sarcoma.

FIGURE S2

Groups were subdivided by post-PEA PVR groups: < 3 Wood units (WU) (n=400), 3-5 WU (n=260), > 5-7 WU (n=102). > 7 WU (n=104). The median score is plotted at each time point. 95% CIs are not displayed to improve visualisation.

FIGURE S3

Correlation matrix for pre- and post-PEA delta change in CAMPHOR score and other outcome variables / markers of disease severity. Pearson correlation coefficient was used to describe associations between complete pairs of outcome / severity variables including CAMPHOR score. Act, activity; CAMPHOR, The Cambridge Pulmonary Hypertension Outcome Review; CI, cardiac index; CTEPH, Chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; QoL, quality of life; Symp, symptoms; WHO FC, World Health Organization functional class; 6MWD, 6-minute walking distance.

FIGURE S4

Kaplan-Meier survival curves of survival time for post-PEA CTEPH patients stratified by change in CAMPHOR activity score from baseline (pre-PEA). Timepoint 0 is the first CAMPHOR score at post-PEA follow-up within a year and survival time is up to 5 years. CAMPHOR change from baseline for the tertiles: highest tertile (-23 to -7), middle tertile (-7 to -3), lowest tertile (-3, 19). Group differences were assessed with a log-rank test.

FIGURE S5

Kaplan-Meier survival curves of survival time for post-PEA CTEPH patients stratified by change in CAMPHOR quality of life (QoL) score from baseline (pre-PEA). Timepoint 0 is the first CAMPHOR score at post-PEA follow-up within a year and survival time is up to 5 years. CAMPHOR change from baseline for the tertiles: highest tertile (-24, -7), middle tertile (-7, -2), lowest tertile (-2, 17). Group differences were assessed with a log-rank test.

FIGURE S6

Kaplan-Meier survival curves of survival time for post-PEA CTEPH patients stratified by change in CAMPHOR symptoms score from baseline (pre-PEA). Timepoint 0 is the first CAMPHOR score at post-PEA follow-up within a year and survival time is up to 5 years. CAMPHOR change from baseline for the tertiles: highest tertile (-25, -10), middle tertile (-10, -5), lowest tertile (-5,20). Group differences were assessed with a log-rank test.

Timepoint	n	CAMPHOR domain		
		Activity	QoL	Symptoms
Baseline	1053	11 ± 9 (11, 12)	11 ± 11 (11, 12)	13 ± 10 (12, 13)
Follow-up 1	934	6 ± 9 (5, 6)	4 ± 11 (3, 4)	4 ± 8 (3, 4)
Follow-up 2	609	5 ± 10 (4, 6)	2 ± 9 (2, 3)	3 ± 10 (3, 4)
Follow-up 3	233	4 ± 10 (3, 6)	2 ± 8 (1, 3)	3 ± 10 (2, 4)
Follow-up 4	194	5 ± 11 (4, 6)	2 ± 10 (1, 4)	4 ± 11 (3, 6)
Follow-up 5	155	4 ± 12 (3, 6)	2 ± 9 (1, 4)	3 ± 10 (2, 5)

TABLE S1

Longitudinal summary of CAMPHOR scores among patients with CTEPH undergoing PEA. The number of patients with CAMPHOR score available at baseline (pre-PEA) and each follow-up 1-5 years following PEA. Data presented as median ± interquartile range (95% CI of median).

Timepoint	CAMPHOR domain					
	Activity		QoL		Symptoms	
	CC	Imputed	CC	Imputed	CC	Imputed
Baseline	11.9 (0.2)	12.0 (0.2)	11.1 (0.2)	11.3 (0.2)	13.1 (0.2)	13.2 (0.2)
Follow-up 1	7.2 (0.2)	7.3 (0.2)	6.1 (0.2)	6.2 (0.2)	5.7 (0.2)	5.8 (0.2)
Follow-up 2	6.7 (0.3)	6.8 (0.3)	5.3 (0.3)	5.5 (0.3)	5.9 (0.3)	5.9 (0.3)
Follow-up 3	6.9 (0.5)	7.2 (0.8)	4.9 (0.4)	5.8 (0.8)	5.6 (0.4)	5.6 (0.6)
Follow-up 4	7.0 (0.5)	8.1 (0.7)	5.4 (0.5)	6.2 (0.7)	6.4 (0.5)	6.4 (0.5)
Follow-up 5	6.6 (0.6)	7.9 (0.8)	5.0 (0.5)	5.8 (0.7)	5.8 (0.5)	6.0 (0.7)

TABLE S2

Longitudinal CAMPHOR score in patients undergoing PEA using multiply imputed data. Data are presented as mean (SE). Pooling of multiply imputed data using Rubin's rules requires continuous data and therefore the mean (SE) has been displayed to enable comparison with the complete cases data. The number of individuals with data available for the complete cases is shown in supplementary table S1 and for the multiply imputed data n=1324 individuals were included. CC, complete cases; Imputed, multiply imputed data.

Variable	No residual PH			Residual PH		
	n	Statistic	95% CI	n	Statistic	95% CI
Age at PEA, Years	685	60 ± 22	58, 61	369	64 ± 20	63, 66
Year of PEA	685	2012 ± 5	2012, 2013	369	2012 ± 4	2012, 2013
Sex, Female	685	288 (42%)		369	182 (49%)	
CAMPHOR: Activity						
Baseline	565	10 ± 9	10, 11	304	13 ± 10	12, 13
Follow-up 1	581	4 ± 9	3, 5	297	9 ± 10	8, 10
Follow-up 2	389	3 ± 8	3, 4	206	8 ± 10	7, 10
Follow-up 3	158	3 ± 8	2, 3	68	10 ± 9	8, 12
Follow-up 4	132	3 ± 9	2, 4	57	10 ± 8	7, 12
Follow-up 5	111	3 ± 7	2, 4	41	11 ± 11	6, 13
CAMPHOR: QoL						
Baseline	565	10 ± 12	9, 11	304	12 ± 10	11, 13
Follow-up 1	581	2 ± 8	1, 2	297	7 ± 11	6, 9
Follow-up 2	388	1 ± 6	1, 2	206	6 ± 10	4, 7
Follow-up 3	157	1 ± 5	0, 2	68	6 ± 10	4, 8
Follow-up 4	132	1 ± 7	0, 2.8	57	6 ± 11	2, 10
Follow-up 5	111	1 ± 5	0, 1	41	7 ± 10	5, 11

CAMPHOR: Symptoms						
Baseline	565	12 ± 10	12, 13	304	13 ± 9	12, 14
Follow-up 1	581	2 ± 7	2, 3	297	7 ± 9	6, 7
Follow-up 2	389	2 ± 7	1, 2	206	7 ± 11	5, 9
Follow-up 3	158	1 ± 7	1, 2	68	8 ± 9	7, 11
Follow-up 4	132	2 ± 8	1, 4	57	10 ± 11	7, 12
Follow-up 5	111	2 ± 6	1, 3	41	10 ± 12	7, 14
WHO FC	656			363		
1		0 (0%)			0 (0%)	
2		103 (16%)			25 (7%)	
3		504 (77%)			298 (82%)	
4		49 (7%)			40 (11%)	
6MWD, Metres	595	320 ± 179	306, 333	309	265 ± 182	240, 285
Haemodynamics						
CI, L/min/m ²	610	2.2 ± 0.8	2.2, 2.2	345	2.1 ± 0.8	2.0, 2.1
mPAP, mmHg	643	43 ± 16	42, 44	351	49 ± 13	47, 50
PVR, WU	623	7.59 ± 6.23	7.21, 8.1	347	9.51 ± 5.33	9.08, 10

TABLE S3

Demographics and characteristics for CTEPH patients with and without clinically significant residual pulmonary hypertension post-PEA. Data presented as median ± interquartile range (95% CI of median) or number of patients (%). The variables are recorded closest to the time of diagnosis and pre-PEA for 6MWD, pulmonary haemodynamics and WHO functional class. CAMPHOR score is recorded at baseline (pre-PEA) and follow-up 1-5 years following PEA. Act, activity; CAMPHOR, The Cambridge Pulmonary

Hypertension Outcome Review; CI, cardiac index; CTEPH, Chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; QoL, quality of life; Symp, symptoms; WHO FC, World Health Organization functional class; WU: Wood units; 6MWD, 6-minute walking distance.

Variable	n	Statistic	95% CI	P value
Age, years	198	69 ± 19	67, 71	<0.0001
Sex, female	198	102 (52)		0.2338
Year of diagnosis	198	2010 ± 5	2009, 2010	<0.0001
CAMPBOR score				
Activity	189	12 ± 11	11, 13	0.345
QoL	190	11 ± 14	9, 11	0.0912
Symptoms	190	12 ± 10	11, 13	0.0484
Haemodynamics				
CI, L/min/m ²	137	1.9 ± 0.7	1.8, 2.0	<0.0001
mPAP, mmHg	134	43 ± 15	41, 45	0.00715
PVR, WU	124	8.28 ± 6.91	7.88, 9.21	0.584

TABLE S4

Demographics and characteristics of the not-operated CTEPH group (n=198) prior to propensity matching. Data presented as median ± interquartile range (95% CI of median) or number of patients (%). The variables are recorded closest to the time of diagnosis for pulmonary haemodynamics, and CAMPBOR score. *P*-values are calculated between not-operated and operated using the PEA cohort summarised in **table 1** with the Mann-Whitney *U* test. CAMPBOR, The Cambridge Pulmonary Hypertension Outcome Review; CI, cardiac index; CTEPH, Chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; QoL, quality of life; WU: Wood units.

Variable	No PEA			PEA		
	n	Statistic	95% CI	n	Statistic	95% CI
Age, Years	132	69 ± 17	66, 71	396	67 ± 13	66, 69
Year of diagnosis	132	2011 ± 4	2011, 2012	396	2011 ± 5	2010, 2011
Sex, Female	132	72 (55%)		396	208 (53%)	
CAMPHOR: Activity						
Baseline	132	11 ± 11	10, 12	396	12 ± 10	11, 13
Follow-up 1	97	10 ± 13	8, 12	308	6 ± 8	5, 7
Follow-up 2	90	9 ± 11	8, 12	223	5 ± 9	3, 6
CAMPHOR: QoL						
Baseline	132	10 ± 13	8, 11	396	10 ± 11	9, 11
Follow-up 1	97	8 ± 13	6, 11	308	3 ± 9	2, 3
Follow-up 2	90	7 ± 10	6, 9	223	1 ± 6	1, 2
CAMPHOR: Symptoms						
Baseline	132	12 ± 12	10, 13	396	11 ± 10	11, 12
Follow-up 1	97	10 ± 12	8, 11	308	3 ± 7	2, 4
Follow-up 2	90	9 ± 12	7, 10	223	2 ± 9	2, 4
WHO functional class						
1	124	0 (0%)		386	0 (0%)	
2		21 (16%)			42 (11%)	
3		91 (70%)			311 (80%)	
4		12 (9%)			33 (8%)	
6MWD, Metres	117	275 ± 167	240, 300	360	283 ± 193	263, 297

Haemodynamics

CI, L/min/m ²	129	1.9 ± 0.7	1.8, 2.0	386	2.1 ± 0.8	2.0, 2.2
mPAP, mmHg	132	43 ± 15	41, 45	396	43 ± 14	41, 43
PVR, WU	121	8.16 ± 6.83	7.71, 9.18	389	7.5 ± 5.79	7.2, 8.26

TABLE S5

Propensity matched group summaries for operated (n= 396) and not operated (n = 132) CTEPH patients. Groups were propensity matched (3:1) by baseline CAMPHOR score, mPAP, age, sex and year of diagnosis. Data presented as median ± interquartile range (95% CI of median) or number of patients (%). The variables are recorded closest to the time of diagnosis for 6MWD, pulmonary haemodynamics and WHO functional class. CAMPHOR score is recorded at baseline and follow-up 1-2 years. N=132 total not operated (Distal = 56, comorbidities = 31, declined = 19, other (combination of factors including limited disease/symptoms) = 26). CAMPHOR, The Cambridge Pulmonary Hypertension Outcome Review; CI, cardiac index; CTEPH, Chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; QoL, quality of life; WHO FC, World Health Organization functional class; WU: Wood units. 6MWD, 6-minute walking distance.

		Activity model		QoL model			Symptoms model		
Terms	unit	OR (95% CI)	P value	Terms	OR (95% CI)	P value	Terms	OR (95% CI)	P value
QoL	1.0	1.19 (1.1, 1.28)	<0.0001	Act	1.20 (1.11, 1.3)	<0.0001	Act	1.41 (1.32, 1.5)	<0.0001
Symp	1.0	1.54 (1.42, 1.67)	<0.0001	Symp	2.03 (1.89, 2.18)	<0.0001	QoL	1.71 (1.62, 1.8)	<0.0001
Sex	M	1.01 (0.55, 1.84)	0.984	Sex	0.99 (0.53, 1.83)	0.97	Sex	1.01 (0.59, 1.73)	0.97
Age	5.0	1.12 (1.01, 1.26)	0.0367	Age	0.83 (0.74, 0.93)	0.00134	Age	0.89 (0.8, 0.98)	0.0151
6MWD	10.0	0.85 (0.82, 0.87)	<0.0001	6MWD	0.97 (0.94, 1.01)	0.107	6MWD	1.01 (0.98, 1.04)	0.462
CI	0.1	1.00 (0.94, 1.07)	0.878	CI	1.00 (0.94, 1.07)	0.912	CI	1.00 (0.94, 1.05)	0.913
mPAP	5.0	0.96 (0.79, 1.18)	0.72	mPAP	1.08 (0.88, 1.33)	0.437	mPAP	0.90 (0.75, 1.08)	0.256
PVR	1	1.03 (0.92, 1.15)	0.594	PVR	1.03 (0.92, 1.16)	0.602	PVR	0.95 (0.86, 1.05)	0.309

TABLE S6

Multivariable linear regression of associations with baseline CAMPHOR score. N=658 individuals including in each model (666 observations removed due to incomplete data). For the units, CI is in L/min/m², mPAP is in mmHg, PVR is in dynes·s·cm⁻⁵. CI, cardiac index; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance (in Wood units); QoL, quality of life; 6MWD, 6-minute walking distance.

	Unit change	HR (95% CI)	P value
CAMPBOR			
Activity	1 point	1.04 (0.97, 1.11)	0.265
QoL	1 point	1.03 (0.98, 1.08)	0.305
Symptoms	1 point	0.99 (0.93, 1.06)	0.782
Age	5 years	1.16 (1.07, 1.26)	0.0006
Sex: Male		0.85 (0.57, 1.27)	0.426
6MWD	10 metres	0.98 (0.95, 1.01)	0.105
Haemodynamics			
Cardiac index	0.1 L/min/m ²	1.00 (0.95, 1.06)	0.993
mPAP	5 mmHg	0.99 (0.86, 1.14)	0.866
PVR	1 WU	1.03 (0.95, 1.11)	0.521

TABLE S7

Cox proportional hazard model of survival 1 year post-PEA in CTEPH using multiply imputed data. The association between baseline, pre-PEA variables and 1 year survival following PEA was assessed. CAMPBOR score, 6MWD and haemodynamics are baseline, pre-PEA. Multiply imputed data was used in this model, which included 1324 individuals and 100 deaths (mean across imputations). 6MWD: 6-minute walk distance; CI: confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; HR: hazard ratio; mPAP: mean pulmonary arterial pressure; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; QoL: quality of life; WU: Wood units.

CAMPHOR	Median $\pm$ IQR	95% CI
Activity	-5 $\pm$ 7	-6, -5
QoL	-5 $\pm$ 9	-5, -4
Symptoms	-7 $\pm$ 7	-8, -6

TABLE S8

Nine month post-PEA landmark analysis of change in CAMPHOR from baseline (pre-PEA). Individuals that had a follow-up CAMPHOR score at least 9 months post-PEA were included in the analysis (n=588). The first available CAMPHOR score after 9 months was used to calculate the change from baseline.

CAMPHOR	Median $\pm$ IQR	95% CI
Activity	-5 $\pm$ 5	-6, -3
QoL	-3 $\pm$ 10	-6, -1
Symptoms	-7 $\pm$ 8	-10, -4

TABLE S9

CAMPHOR MCID was calculated from the 6MWD MCID that has previously been defined for PAH [2]. CTEPH patients with an improvement in 6MWD from baseline (pre-PEA) to follow-up within a year of PEA of between 25.1 and 38.6m (n=42) were included in the analysis. The CAMPHOR change from baseline represented the CAMPHOR MCID.

	n	Activity	QoL	Symptoms
No concurrent surgery	140	-3 ± 5 (-4, -3)	-5 ± 8 (-6, -3)	-7 ± 8 (-8, -6)
No Cancer	124	-3 ± 5 (-4, -2)	-4 ± 8 (-6, -3)	-6 ± 7 (-8, -5)
PVR				
< 3 WU	66	-3 ± 6 (-5, -2)	-6 ± 8 (-8, -4)	-8 ± 8 (-8, -6)
3-5 WU	44	-3 ± 4 (-4, -2)	-3 ± 6 (-4, -2)	-6 ± 9 (-7, -5)
5-7 WU	16	-4 ± 6 (-7, -2)	-1 ± 8 (-7, 0)	-8 ± 5 (-10, -5)
> 7 WU	15	-2 ± 5 (-5, 0)	-4 ± 9 (-9, 0)	-6 ± 9 (-11, -1)

TABLE S10

Sensitivity analyses of the MCID in CAMPHOR score for patients with CTEPH undergoing PEA using an anchor method. Data are median ± IQR (95% CI). The change from baseline (pre-PEA) in CAMPHOR score at 1 year post PEA, in relation to ratings to a global health status change question. The “no concurrent surgery” group (n=588) are those that did not have additional surgery procedures (e.g. ASD/PFO closure, AVR, CABG or MVR) during the PEA operation. The “no cancer” group were those *without* a comorbidity of cancer recorded (n=519). The PVR groups have been stratified by PVR at baseline pre-PEA (n=592). The “n” in each group represents the number of individuals in that category that have baseline and post-PEA CAMPHOR scores available along with a global health status change recorded as “moderately better”, which was used to define the MCID.

	CAMPHOR: Activity			
	Below MCID (n=257)		Above MCID (n=527)	
	Pre-PEA	Post-PEA	Pre-PEA	Post-PEA
Age , years	62 ± 19		62 ± 22	
Women , n (%)	125 (49)		235 (45)	
Year of PEA	2013 ± 4		2012 ± 5	
CAMPHOR				
Activity	8 ± 8	10 ± 11	13 ± 9	4 ± 7
QoL	8 ± 11	7 ± 12	12 ± 10	2 ± 8
Symptoms	10 ± 11	6 ± 11	14 ± 8	3 ± 7
WHO FC , n (%)				
1	2 (1)	52 (21)	7 (1)	176 (34)
2	42 (17)	109 (44)	52 (10)	232 (45)
3	192 (76)	82 (33)	416 (80)	100 (20)
4	16 (6)	4 (2)	43 (8)	3 (1)
6MWD , metres	303 ± 186	342 ± 188	300 ± 186	370 ± 152
NT-proBNP , pg/mL	587 ± 1601	258 ± 522	715 ± 2216	195 ± 327
Haemodynamics				
CI, L/min/m ²	2.13 ± 0.74	2.2 ± 0.72	2.1 ± 0.78	2.32 ± 0.66
mPAP, mmHg	44 ± 16	27 ± 15	46 ± 15	24 ± 12
PVR, WU	7.58 ± 6.27	3.45 ± 3.06	8.8 ± 5.64	2.98 ± 2.53
PCWP, mmHg	11 ± 6	11 ± 5	11 ± 5	10 ± 5
RAP, mmHg	9 ± 7	7 ± 6	10 ± 7	6 ± 4
Type of surgical disease , n (%)				
1	21 (9)		83 (17)	
2	150 (63)		294 (60)	
3	66 (28)		115 (23)	
4	1 (0)		1 (0)	
Cardiac bypass time , minutes	326 ± 62		321 ± 74	
Arrest time , minutes	38 ± 15		37 ± 14	
Length of stay , days				
Intensive care unit	4 ± 3		4 ± 3	
Total hospital	15 ± 10		14 ± 10	

TABLE S11

Responder analysis for CTEPH patients above (“responders”) and below the CAMPHOR activity MCID of -3. Data are median $\pm$ IQR or n (%). There were 257 CTEPH patients below the CAMPHOR activity MCID (“non-responders”) and 527 above (“responders”) from a total of 784 patients that had both pre- and post-PEA CAMPHOR scores. 6MWD: 6-minute walk distance; CI: cardiac index; CTEPH: chronic thromboembolic pulmonary hypertension; IQR: interquartile range; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCWP: pulmonary capillary wedge pressure; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WHO FC: World Health Organization Functional Class; WU: Wood units.

	QoL			
	Below MCID (n=347)		Above MCID (n=437)	
	Baseline	Follow-up	Baseline	Follow-up
Age, years	63 ± 19		62 ± 25	
Women, n (%)	166 (48)		194 (44)	
Year of PEA	2013 ± 5		2012 ± 5	
CAMPHOR				
Activity	9 ± 10	8 ± 11	12 ± 9	5 ± 7
QoL	6 ± 11	7 ± 14	13 ± 8	2 ± 6
Symptoms	10 ± 10	6 ± 11	14 ± 8	3 ± 6
WHO FC, n (%)				
1	2 (1)	84 (25)	7 (1)	144 (34)
2	50 (15)	139 (42)	44 (10)	202 (48)
3	265 (78)	106 (32)	343 (80)	76 (18)
4	25 (7)	5 (2)	34 (8)	2 (1)
6MWD, metres	320 ± 197	357 ± 179	292 ± 185	370 ± 148
NT-proBNP, pg/mL	492 ± 1403	233 ± 473	934 ± 2377	195 ± 315
Haemodynamics				
CI, L/min/m ²	2.1 ± 0.73	2.25 ± 0.71	2.1 ± 0.8	2.31 ± 0.68
mPAP, mmHg	44 ± 17	26 ± 14	46 ± 14	24 ± 11
PVR, WU	7.6 ± 5	3.29 ± 3.26	9 ± 5.68	3 ± 2.38
PCWP, mmHg	11 ± 5	11 ± 6	11 ± 5	10 ± 5
RAP, mmHg	9 ± 6	7 ± 5	10 ± 8	6 ± 5
Type of surgical disease,				
n (%)				
1	40 (12)		64 (16)	
2	197 (61)		247 (61)	
3	85 (26)		96 (24)	
4	2 (1)		0 (0)	
Cardiac bypass time, minutes	324 ± 61		320 ± 75	
Arrest time, minutes	37 ± 14		37 ± 17	
Length of stay, days				
Intensive care unit	4 ± 3		4 ± 3	
Total hospital	15 ± 12		14 ± 9	

TABLE S12

Responder analysis for CTEPH patients above (“responders”) and below the CAMPHOR QoL MCID of -4. Data are median $\pm$ IQR or n (%). There were 347 CTEPH patients below the CAMPHOR activity MCID (“non-responders”) and 437 above (“responders”) from a total of 784 patients that had both pre- and post-PEA CAMPHOR scores. For abbreviations see **supplementary table S11**.

	Symptoms			
	Below MCID (n=303)		Above MCID (n=481)	
	Baseline	Follow-up	Baseline	Follow-up
Age , years	62 ± 20		62 ± 22	
Women , n (%)	137 (45)		223 (46)	
Year of PEA	2013 ± 5		2012 ± 5	
CAMPHOR				
Activity	9 ± 10	8 ± 11	13 ± 9	5 ± 7
QoL	8 ± 10	5 ± 13	13 ± 9	2 ± 8
Symptoms	8 ± 10	6 ± 12	15 ± 8	3 ± 6
WHO FC , n (%)				
1	4 (1)	69 (24)	5 (1)	159 (34)
2	42 (14)	130 (45)	52 (11)	211 (45)
3	230 (77)	90 (31)	378 (80)	92 (20)
4	21 (7)	2 (1)	38 (8)	5 (1)
6MWD , metres	310 ± 174	357 ± 164	299 ± 189	370 ± 156
NT-proBNP , pg/mL	447 ± 1321	251 ± 509	938 ± 2360	189 ± 314
Haemodynamics				
CI, L/min/m ²	2.1 ± 0.75	2.22 ± 0.73	2.1 ± 0.81	2.31 ± 0.65
mPAP, mmHg	44 ± 16	26 ± 15	46 ± 15	24 ± 12
PVR, WU	7.82 ± 5.76	3.29 ± 3.49	8.79 ± 6.07	3 ± 2.44
PCWP, mmHg	11 ± 5	11 ± 6	11 ± 5	10 ± 5
RAP, mmHg	9 ± 8	7 ± 6	9 ± 7	6 ± 5
Type of surgical disease ,				
n (%)	33 (12)		71 (16)	
1	169 (60)		275 (61)	
2	80 (28)		101 (23)	
3	1 (0)		1 (0)	
4				
Cardiac bypass time , minutes	324 ± 61		320 ± 75	
Arrest time , minutes	36 ± 13		37 ± 17	
Length of stay , days				
Intensive care unit	4 ± 4		4 ± 3	
Total hospital	15 ± 11		14 ± 9	

TABLE S13

Responder analysis for CTEPH patients above (“responders”) and below the CAMPHOR symptoms MCID of -6. Data are median $\pm$ IQR or n (%). There were 303 CTEPH patients below the CAMPHOR activity MCID (“non-responders”) and 481 above (“responders”) from a total of 784 patients that had both pre- and post-PEA CAMPHOR scores. For abbreviations see **supplementary table S11**.

	Unit change	HR (95% CI)	P value
CAMPHOR			
Activity	1 point	1.03 (0.95, 1.11)	0.530
QoL	1 point	1.06 (0.97, 1.15)	0.230
Symptoms	1 point	0.96 (0.87, 1.06)	0.394
Age	5 years	1.15 (1, 1.33)	0.0569
Sex: Male		0.50 (0.24, 1.04)	0.0634
6MWD	10 metres	0.97 (0.94, 1.01)	0.103
Haemodynamics			
Cardiac index	0.1 L/min/m ²	0.99 (0.91, 1.08)	0.774
mPAP	5 mmHg	0.88 (0.69, 1.13)	0.317
PVR	1 WU	1.07 (0.95, 1.22)	0.253
PCWP	1 mmHg	1.06 (0.98, 1.15)	0.122

TABLE S14

Cox proportional hazards model of baseline variables and survival 1 year post-PEA in CTEPH using complete cases. This model is the same as presented in **table 4**, with the addition of the variable PCWP. CAMPHOR score, 6MWD and haemodynamics are baseline, pre-PEA. Complete cases data was used for this cox proportional hazard model, which included 550 individuals and 35 deaths (774 observations were removed due to incomplete data). 6MWD: 6-minute walk distance; CI: confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; HR: hazard ratio; mPAP: mean pulmonary arterial pressure; PEA: pulmonary endarterectomy; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; QoL: quality of life; WU: Wood units.

		CC		Imputed	
	Unit change	HR (95% CI)	P value	HR (95% CI)	P value
CAMPHOR					
Activity	1 point	0.94 (0.88, 1.01)	0.1	0.97 (0.93, 1.01)	0.112
QoL	1 point	1.07 (0.99, 1.14)	0.0831	1.02 (0.98, 1.06)	0.457
Symptoms	1 point	1.00 (0.93, 1.08)	0.923	0.99 (0.96, 1.03)	0.759
Age	5 years	1.40 (1.21, 1.6)	<0.0001	1.23 (1.16, 1.3)	<0.0001
Sex: Male		0.81 (0.47, 1.42)	0.469	0.76 (0.58, 0.99)	0.0404
6MWD	10 metres	0.97 (0.94, 1.01)	0.183	0.99 (0.96, 1.02)	0.39
Haemodynamics					
Cardiac index	0.1 L/min/m ²	0.98 (0.93, 1.03)	0.409	0.99 (0.96, 1.02)	0.554
mPAP	5 mmHg	1.07 (0.9, 1.28)	0.438	1.15 (1.04, 1.27)	0.0048
PVR	1 WU	0.98 (0.86, 1.11)	0.737	0.96 (0.9, 1.03)	0.249

TABLE S15

Cox proportional hazard model of long-term survival post-PEA in CTEPH. The association between change from baseline variables and long-term survival was assessed. CAMPHOR score, 6MWD and haemodynamics are the change from baseline (pre-PEA) to follow-up (post-PEA) within a year. The complete cases data used in this model included 461 individuals and 52 deaths (863 observations were deleted due to missingness). The multiply imputed ("Imputed") data used in this model included 1324 individuals and 252 deaths (mean across imputations) over 5 years. 6MWD: 6-minute walk distance; CC: complete cases; CI: confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; HR: hazard ratio; mPAP: mean pulmonary arterial pressure; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; QoL: quality of life; WU: Wood units.

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