Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the UK national cohort

First Author's surname and short title: Cannon, Pulmonary endarterectomy long term outcome

Authors: Cannon JE[1], MRCP PhD; Su L[2], PhD; Kiely DG[3], MD; Page K[1], BSc; Toshner M[1], MD; Swietlik E[1,4], MD; Treacy C[1], BSc; Ponnaberanam A[1], RGN; Condliffe R[3], MD; Sheares KK[1], FRCP, PhD; Taboada D[1], MD; Dunning JJ[1], FRCS, Tsui SSL[1], MD, FRCS, Ng C[1], FRCS, Gopalan D[5], FRCR; Screaton N[1], FRCR; Elliot CA[3], MD; Gibbs JSR[5], Howard LS[5], FRCP; MD; Corris PA[6], FRCP; Lordan JL[6], FRCP; Johnson MJ[7], MD Peacock AJ[7], MD; MacKenzie Ross R[8], MRCP; Schreiber[8], MD, Coghlan JG[9], MD; Dimopoulos K[10], MD; Wort SJ[10], FRCP PhD; Gaine S[11], MD, Moledina S[12], MBChB; Jenkins DP[1], FRCS; and Pepke-Zaba J[1], MD PhD.

Affiliations: [1] Papworth Hospital, Cambridge, UK; [2] MRC Biostatistics Unit, Cambridge, UK; [3] Royal Hallamshire Hospital, Sheffield UK; [4] Respiratory Medicine Department, University of Warmia and Mazury, Poland; [5] Hammersmith Hospital, London, UK, [6] Freeman Hospital, Newcastle, UK; [7] Golden Jubilee Hospital, Glasgow, UK; [8] Royal United Hospital, Bath, UK; [9] Royal Free Hospital, London, UK; [10] Royal Brompton Hospital, London, UK; [11] Mater Misericordiae University Hospital, Dublin, Ireland; [12] Great Ormond Street Hospital, London, UK

Corresponding author: Joanna Pepke-Zaba, Papworth Hospital, Papworth

Everard, Cambridge, CB23 3RE, UK. Tel: +44 1480 364230, Fax: +44 1480 364267. email: joana.pepkezaba@papworth.nhs.uk

Journal Subject Codes: [14] other hypertension

Word count: 7046

Abstract

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) results from incomplete resolution of pulmonary emboli. Pulmonary endarterectomy (PEA) is potentially curative, but residual PH following surgery is common and its impact on long-term outcome is poorly understood. We wanted to identify factors correlated with poor long-term outcome after surgery and specifically define clinically relevant residual PH post-PEA.

Methods and Results: 880 consecutive patients (mean age 57 years) underwent PEA for CTEPH. Patients routinely underwent detailed re-assessment with right heart catheterisation and non-invasive testing at 3-6 months and annually thereafter with discharge if clinically stable at 3-5 years and not requiring pulmonary vasodilator therapy. Cox regressions were used for survival (time-to-event) analyses. Overall survival was 86%, 84%, 79% and 72% at 1, 3, 5 and 10 years for the whole cohort and 91% and 90% at 1 and 3 years for the recent half of the cohort. The majority of patient deaths after the peri-operative period were not due to right ventricular failure (CTEPH). At reassessment a mean pulmonary artery pressure (mPAP) $\geq$ 30 mmHg correlated with pulmonary vasodilator therapy initiation post-PEA. An mPAP $\geq$ 38 mmHg and pulmonary vascular resistance $\geq$ 425 dyne/sec/cm^{-5} at reassessment correlated with worse long-term survival.

Conclusions: Our data confirm excellent long-term survival and maintenance of good functional status post-PEA. Haemodynamic assessment 3-6 and/or 12 months post-PEA allows stratification of patients at higher risk of dying

from CTEPH and identifies a level of residual pulmonary hypertension which may guide the long-term management of patients post-surgery.

Key Words: Pulmonary Hypertension, pulmonary endarterectomy, pulmonary embolism, survival

Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of acute pulmonary emboli (PE) with uncertain prevalence, ranging from 0.57 to 9.1%.[1] The diagnosis is strongly associated with a history of acute venous thromboembolism.[2] CTEPH results from incomplete resolution of PE which become organised into vessel walls and cause different degrees of obstruction to pulmonary blood flow. Increased pulmonary vascular resistance (PVR) leads to increased right ventricular pressure load and eventually to right ventricular failure. Historically the long-term outlook was poor with 5-year survival rates as low as 10%.[3] Pulmonary endarterectomy (PEA) is the treatment of choice and in selected patients is curative.[4] It is recognised that there is a steep surgical and institutional learning curve at the start of a PEA program, but in experienced centres the operative mortality rate is less than 5%.[5-7] A number of reports have confirmed improved short-term outcome in terms of haemodynamics, right ventricular function, quality of life, functional status and exercise capacity after surgery.[7-18] Fewer reports describe long-term outcome post-PEA and those that have been published are mainly retrospective and either only had small numbers of patients [19-26] or limited information of factors correlated with long-term outcome. [6, 27-31]

CTEPH is described by a two compartmental model with proximal vessel obstruction that is surgically accessible and a small vessel arteriopathy found in non-obstructed vessels, which is histologically similar to pulmonary arterial hypertension (PAH) and cannot be removed by surgery. [32, 33] This model explains why residual pulmonary hypertension (PH) can occur despite an

apparently successful surgical clearance. Depending on the definition used, between 11% and 35% of patients have residual PH following PEA.[14, 25, 28-30] Evidence suggests that long-term outcomes are dependent on post-operative haemodynamics. [6, 7, 12, 17, 23, 34] Persistently increased PVR greater than 500 dyne/sec/cm^{-5} at the end of intensive care unit (ICU) stay is a significant risk factor for in-hospital death and mortality during the first year post-PEA. [6, 7, 12, 34] PVR measured between 3 and 12 months after PEA can predict longer-term outcome. [17, 23] In contrast, patients found to have a mean pulmonary artery pressure (mPAP) greater than 30 mmHg at follow-up had a smaller increase in exercise capacity, but no difference in survival at 4 years when compared to patients with an mPAP less than 30 mmHg after surgery. [29] In addition, a recent trial has shown an improvement in exercise capacity in patients with CTEPH that are inoperable or have persistent PH post PEA [35] therefore further information on the natural history of disease would be helpful in identifying a low risk group who might not require drug therapy.

The understanding of post-PEA haemodynamics and the consequences for patient management is thus incomplete. There is no consensus on the definition of residual (i.e. PH immediately after surgery or at early post-operative follow-up when the remodelling of right ventricle is completed) or recurrent PH (i.e. when there is no PH on first assessment but then PH is identified subsequently). We present prospectively obtained long-term data from the United Kingdom (UK) national PEA cohort to identify the factors correlated with worse long-term outcome and specifically define what is clinically relevant PH, both residual and recurrent, after PEA.

Methods

Study design

Eight designated PH specialist centres from the UK and Mater Misericordiae University Hospital, Dublin, Ireland undertake the diagnosis and management of all CTEPH patients in these countries. All CTEPH patients are referred for consideration of PEA. Of importance, only designated PH centres can prescribe pulmonary vasodilator therapies. This system of care provides a unique opportunity to study the natural history of the disease following surgical intervention through the careful follow-up of a national cohort of all CTEPH patients. All data were entered prospectively into dedicated databases at Papworth Hospital and the other UK and Ireland specialist PH centres. This study was designed and conducted to describe current care therefore formal ethics approval was not required. The National Health Service (NHS) Health Research Authority Confidentiality Group was fully informed regarding the use of patient data.

Patient selection

Patient selection was as previously described.[29] Consecutive patients who underwent PEA at Papworth Hospital from the first operation in January 1997 until December 31st 2012 were included in this study with the exception of patients with chronic thromboembolic disease without PH (mPAP < 25 mmHg)

[36] and those with conditions mimicking CTEPH e.g. pulmonary artery vasculitis or sarcoma.

Surgical Technique

PEA was performed using principles similar to those used by the University of California, San Diego group. [6, 34] All patients underwent surgical intervention with deep hypothermia, but complete arrest of the circulation was not used in all cases. [37, 38] Surgical specimens were classified into four types according to the Jamieson classification.[39] Patients continued lifelong anticoagulation after surgery.

Clinical assessment after surgery and long term follow up

Pulmonary haemodynamics were recorded at 7 am on the first day after surgery and were routinely monitored until patients were extubated. At the start of the program, in those who had poor pre-operative haemodynamics and were in World Health Organisation (WHO) functional class III and IV, the decision to continue ‘bridging’ pulmonary vasodilator therapy was made on reviewing the ICU haemodynamics. With institutional experience, 'bridging' treatment is routinely stopped at the time of the surgery unless the pre-operative haemodynamics were poor and there had been an unsatisfactory surgical clearance. Patients were followed up at Papworth Hospital at 3-6 and 12 months post-PEA as previously described.[29] Following their 12-month

post-PEA review patients were solely followed up by their referring PH centre. These teams managed the patients according to international guidelines including the need for additional right heart catheterisation (RHC) depending on clinical status and non-invasive tests. They also initiated pulmonary vasodilator therapy according to the UK national PH treatment guidelines, which allow off-license treatment of CTEPH patients in functional class (FC) II (only as part of a clinical trial), III or IV. Patients were usually discharged from PH specialist centre follow-up after 5 years if the patient had good surgical clearance, remained in good FC (I or II) and did not require pulmonary vasodilator therapy.

Long term survival assessment

Survival after discharge from hospital was calculated using a censoring date of last review, transplant (n=1) or 11th September 2013, whichever was latest. The NHS summary care record tracking system was used for survival status (searched 11th September 2013). The causes of death were obtained from local databases and from the England or Scotland General Register Offices. The causes of death were independently classified into four groups by three independent adjudicators (JEC, MT & JPZ). Discrepancies in the classification of death were discussed by the adjudicators to reach a consensus. The four groups were: 1) Post-operative death i.e. related to surgery e.g. reperfusion pulmonary oedema, multi-organ failure; 2) Death caused by CTEPH (CTEPH direct) i.e. right ventricular failure away from the operative period; 3) Death

related to CTEPH management (CTEPH related) e.g. due to anticoagulation and 4) Unrelated to CTEPH e.g. malignancy.

Statistical analysis

Statistical analyses were carried out using SAS (version 9.3, SAS institute, Cary, NC) and R (http://cran.r-project.org). Summary statistics (mean ± standard deviation) were calculated and paired t-tests and Wilcoxon signed rank sum tests performed to test the differences in baseline and post-surgery (3-6 months) patient characteristics. Kaplan-Meier curves were created for overall survival by cohort and treatment initiation. Cumulative incidence functions of cause-specific mortality were estimated taking competing risks into account. [40]

Cox regression methods were used to analyse the time to treatment initiation after PEA and the survival time after hospital discharge (all causes). The time scale was the time since PEA surgery. Due to left truncation at hospital discharge for long-term survival analysis, the hospital length of stay was adjusted for in Cox models. Further haemodynamic, FC and six-minute walk distance (6MWD) measured at follow-up visits were included as time-varying covariates in Cox regression models to examine their temporal associations with time to treatment initiation and long-term survival. Proportional hazard assumptions were checked by Schoenfeld residuals in univariable analyses. [41]

To facilitate interpretations, we chose the best threshold values for mPAP, PVR and cardiac index (at follow-up visits) based on the largest likelihood ratio test statistics obtained in separate Cox regressions for time to treatment initiation (with other factors adjusted for, see Figure 2 legend) and CTEPH-direct deaths after hospital discharge (no adjustment was made due to the smaller number of CTEPH-direct deaths observed). [42] In addition, graphical diagnostics on the functional forms of the relationships between log hazard ratios and mPAP, cardiac index and PVR were performed to evaluate the plausibility of the chosen best threshold values. Results of these categorized mPAP, PVR and cardiac index (based on best threshold values and clinical meaningful threshold values) were presented in the univariable and multivariable Cox regression analyses for long-term survival.

Results

Study cohort

From 1997, until the end of 2012, a total of 880 consecutive patients with CTEPH underwent PEA at Papworth Hospital. The mean age was 57 ± 15 years (range 15-84) and 53% were male. The mean baseline mPAP was 47 ± 11 mmHg, PVR 830 ± 382 dyne/sec/cm^{-5} and 6MWD 260 ± 126 m. Pre-surgery, 91% patients were in FC III or IV and 64% patients were taking at least 1 pulmonary vasodilator therapy as a "bridge to surgery" (Table 1). There was a history of malignancy or myeloproliferative disorder in 12.8%,

antiphospholipid syndrome in 4.3%, and splenectomy in 2.8% of patients at time of surgery (Table S1). There were significant improvements in haemodynamic variables, FC and exercise capacity post-surgery (Table 1). Despite this, only 28% of patients had an mPAP $\leq$ 20 mmHg, while 21% had mPAP 21-24 mmHg and 51% had mPAP $\geq$ 25 mmHg at the 3-6 month review. The mean follow-up of patients post-PEA was 4.3 $\pm$ 3.6 years (range 0-15.5 years).

Initiation of pulmonary vasodilator therapy during long-term follow up

Post-PEA, 187 patients were treated with 1 or more pulmonary vasodilator therapies. Of these, 45 patients who were “bridged” continued therapy post-PEA long-term, while 142 patients were initiated on therapy after surgery, with the majority being started as the result of the first post-PEA review (Fig. 1). In univariable Cox regressions a number of demographic, functional and haemodynamic factors correlated with increased risk of treatment initiation during follow-up (Table S2). In multivariable Cox regressions (Table 2), we re-examined the associations of treatment initiation for significant factors identified by univariable analyses. The associations of functional and haemodynamic variables at referral for PEA and over time post-PEA with treatment initiation remained statistically significant (p-values <0.05 except for cardiac index (over time) with a borderline p-value of 0.067) in multivariable analyses (Table 2). Additional analyses using a binary outcome of mPAP≥25 mmHg at the first reassessment after hospital discharge had similar findings to those from the analyses for time to treatment initiation (Tables S3 & S4).

The best threshold values for pulmonary vasodilator therapy initiation over long-term follow-up were identified for mPAP, cardiac index and PVR as being 30 mmHg, 2.14 L/min/m^2 and 318 dyne/sec/cm^{-5} respectively. However, the graphical evidence in Figure S2 indicates that there was a rapid increase in log hazard ratio for treatment initiation for mPAP between 25 to 30 mmHg and after 30 mmHg the log hazard ratio started to plateau. This data analysis suggests that 30 mmHg is a plausible threshold and therefore patients with an mPAP ≥ 30 mmHg were at risk of a deteriorating functional status, which triggered pulmonary vasodilator therapy initiation. We propose this value represents clinically significant PH post-PEA and that these patients need for close long-term follow-up. No apparent patterns were observed for cardiac index and PVR.

Recurrent PH and pulmonary emboli during long-term observation period

Only 5 out of whole observed cohort who had an mPAP < 25 mmHg at their 3-6 month re-evaluation went onto develop PH (mPAP ≥ 25 mmHg), had a clinical deterioration and were started on pulmonary vasodilator therapy during follow-up (Table S5). Of these only 2 patients had recurrent CTEPH without other causes e.g. recurrent PE or different cause for PH. To investigate the frequency of recurrent thromboembolism as the cause of recurrent or worsening pulmonary hypertension, we undertook an additional sub-analysis of patients managed locally by Papworth Hospital in the long-

term. Six out of 356 patients suffered recurrent PE. Of these, all had an inferior vena cava filter in-situ and four had underlying antiphospholipid syndrome.

Survival

There were 174 deaths during a mean follow-up period of 4.3 ± 3.6 years. The survival rates at 1, 3, 5 and 10 years were 86%, 84%, 79% and 72% respectively for the entire cohort from 1997 (Figure 2a). 92/174 (53%) of all deaths were classified as post-operative (Table S6). The cumulative occurrence of 30-day mortality improved significantly over time from 13.2% (95% confidence interval (CI) = [10.2%, 16.3%]) for the first half of our cohort to 2.4% (95%CI=[0.1%, 4.8%]) for the latest part of our cohort of patients undergoing PEA (Figure 2b). The overall survival rates at 1 and 3 years after surgery for the second half of our cohort were 91% and 90%, respectively (Figure 2c). This is despite the proportion of patients found to have the more 'distal' bilateral type 3 thromboembolic disease at the time of surgery increasing from 8% in 2003 to 19% in 2012.

For those patients who survived surgery, but died during the follow-up period: 29/82 (35%) of deaths were classified as directly caused by CTEPH, 13 (16%) were related to CTEPH and 40 (49%) were due to unrelated causes (Figure 2d and Tables S6-8).

Factors correlated with long-term survival

We wanted to understand the post-operative factors correlated with long-term survival. We, like others, have used day 1 post-PEA haemodynamic data as an indicator of haemodynamic response from PEA. There was only a moderate correlation between the day 1 and 3-6 month post-PEA mPAP (r=0.53) and PVR (r=0.57) (Fig. S1 A & B), but a stronger association between the 3-6 and 12 month post-PEA mPAP (r=0.75) and PVR (r=0.79) (Figure S1C & D). The 3-6 month haemodynamic measurements were therefore used for further analyses.

A number of demographic, functional, haemodynamic factors and co-morbidities including malignancy and atrial arrhythmias were identified in univariable Cox regressions to be correlated with long-term survival (Figure 3 and Table S9). In multivariable analyses (Table 3) we individually re-examined the associations of long-term survival for the significant factors identified in univariable analyses after adjusting for other important factors (gender, age, baseline BMI, prior history of malignancy or myeloproliferative disorder and hospital length of stay). Post-operative pulmonary vasodilator therapy initiation, worse FC, shorter 6MWD, higher mPAP, right atrial pressure (RAP) and PVR, lower cardiac index remained negatively correlated with long-term survival in multivariable analyses. An mPAP $\geq$ 36 mmHg and a PVR $\geq$ 416 dyne/sec/cm^{-5} (as time-varying measures) were the optimal thresholds correlated with a higher risk of death from any cause whereas an mPAP $\geq$ 38 mmHg and a PVR $\geq$ 425 dyne/sec/cm^{-5} identified those patients at higher risk of death due to CTEPH. The graphical diagnostics (Figure S2)

confirmed the plausibility of mPAP ≥ 38 mmHg as the threshold as there was a rapid increase in log hazard ratio between 35-38 mmHg before the log hazard ratio plateaued.

Discussion

This is the largest prospective national cohort study describing long-term outcomes post-PEA using a planned invasive haemodynamic evaluation and systematic long-term follow-up. Our study has a number of important messages: 1. risk stratification of patients using invasive haemodynamic measurements at 3-6 and/or 12 months post-PEA can guide which patients need close long-term follow-up to identify clinical deterioration and need for additional treatment; 2. the majority of deaths following the immediate post-operative period were not due to right ventricular failure (CTEPH); 3. long-term survival post-PEA is excellent and most patients maintain a good functional status. It was previously described that PEA results in excellent long-term survival and our data confirms this despite an older or comparable age at the time of surgery in our cohort than other series. [4, 23, 31, 43] Despite significant functional improvement following surgery with 85% of patients in either FC I or II, only 28% of patients had an mPAP ≤ 20 mmHg while 51% had an mPAP ≥ 25 mmHg when measured by RHC at 3-6 months post-PEA. The majority of patients in our cohort maintained a good functional status in the long-term despite residual PH by definition.

<u>The role of post-PEA haemodynamics in long-term patient management</u>

There is no consensus on the definition of clinically significant residual PH post-PEA. Different centres apply a different definition depending on the local patient pathway. Our planned, systematic invasive haemodynamic evaluation in all UK patients over the first year post-surgery contrasts with others who base their post-operative outcome assessment on haemodynamics obtained immediately after PEA, while the patient is in ICU. [6, 12] We only found a moderate correlation between the day 1 ICU haemodynamics and the 3-6 month measurements. A much stronger correlation existed between the 3-6 and 12-month measurements. In our unit, we only record the day 1 ICU haemodynamics as stable patients have their Swan-Ganz catheter removed soon after, preventing later routine measurements in all patients. In comparison the Vienna group (n=110) [23] showed post-operative haemodynamics measured 4 days (mean) post-PEA, when patients were off inotropes, were very similar to those assessed at 1 year post-PEA.

Pulmonary vasodilator therapy for residual PH after PEA

This is the first study to report on factors correlated with pulmonary vasodilator therapy initiation post-PEA. 187 patients in our cohort were treated with pulmonary vasodilator therapy during a mean follow-up period of 4.3 years. The majority were started soon after their 3-6 or 12 month post-PEA evaluations. A number of factors were independently correlated with their initiation including worse FC and 6MWD and higher mPAP and RAP. Post-operative transfer co-efficient of the lung for carbon monoxide (TLco) also negatively correlated with the need to start pulmonary vasodilator therapy.

An arbitrary mPAP threshold of 30 mmHg, based on historical survival data, [3, 44] was previously used by our group to analyse conditional long-term survival. [29] In the current study, we also propose clinically significant PH post-PEA as an mPAP ≥ 30mmHg. In contrast to our previous study, this threshold is the result of an analysis of systematic clinical and haemodynamic data collected during the long-term follow-up of our large cohort of consecutive patients. This discussion of post-operative haemodynamics is currently specifically relevant because the first licensed therapy for the treatment of residual/recurrent PH post-PEA, Riociguat, is now available. In the CHEST-1 trial, 28% of patients included had residual/recurrent PH after PEA. [35] Although the inclusion criteria included an mPAP ≥ 25 mmHg and PVR > 300 dyne/sec/cm^{-5} the mean haemodynamics for the subgroup of patients with recurrent/residual PH post-PEA was 39 mmHg and PVR 595 dyne/sec/cm^{-5}. [45] In our cohort 397 patients would have met the entry criteria for the CHEST-1 trial, but only 174 were treated off-licence with other pulmonary vasodilator therapy while the other 223 patients have remained in a good FC (I or II) during careful follow up by specialist PH physicians. Our data suggest that patients tolerated these haemodynamics well without evidence of deterioration. Our data analysis suggested an mPAP ≥ 30 mmHg was a plausible threshold that identified patients in this study likely to be started on pulmonary vasodilator therapy due to clinical deterioration during long-term follow-up. Other haemodynamic variables including PVR and cardiac index could be used to define clinically significant PH post-PEA. The evidence from our data only suggests a likely change in log-hazard ratios for treatment initiation at an mPAP ≥ 30 mmHg (Figure S2). We therefore propose that an mPAP ≥ 30 mmHg represents

clinically significant residual PH post-PEA and should guide clinicians which patients need close long-term follow-up after surgery.

Our approach to start pulmonary vasodilator therapy post-PEA was conservative due to the limited evidence of effectiveness in this group of patients during the study. Due to the observational nature of our study and lack of a control group we were unable to determine whether they had any effect on survival. Pulmonary vasodilator therapy initiation was however independently correlated with poorer long-term survival. Similar results have recently been reported from an international CTEPH registry. [31] A potential bias with the factors correlated with pulmonary vasodilator therapy initiation post-PEA is that there were no fixed initiation criteria. However, in the UK pulmonary vasodilator therapy prescribing in CTEPH is limited to patients in FC III or IV (unless the patient is enrolled in a clinical trial) according to the UK National PH prescribing policy.

Residual/recurrent CTEPH

Only 5 patients developed recurrent PH (mPAP $\geq$ 25 mmHg) during follow-up. There were only 2 patients who had true recurrent CTEPH without new thromboembolic disease or other cause for PH. These patients presented 9 and 10 years post-surgery and in both patients there was evidence of ongoing mosaic changes seen on computed tomography at their first re-evaluation post-PEA. This would suggest an ongoing disease process involving distal pulmonary arteries, which we hypothesise, progressed over time leading to recurrent CTEPH. The length of time after surgery that these patients re-

presented is important because our mean follow-up was 4.3 years and only 81 patients had 10-year follow-up. Therefore it will be important to continue close follow up of the 223 patients in our cohort with mild residual PH post-PEA, who currently remain in FC I or II without pulmonary vasodilator therapy.

Post-operative long-term mortality

In our cohort over half of the deaths were due to recognised complications in the post-operative period, with the highest proportion in the early part of the series. The 30-day mortality rate in the latest part of our cohort was 2.4%, which is comparable with other expert centres around the world.[5-7] The majority of patient deaths during long-term follow-up were from other conditions rather than progressive right ventricular failure (CTEPH direct deaths). Ideally it would have been better to investigate the combined factors correlated with CTEPH direct deaths rather than all-cause mortality after surviving the operative period, but due to the small numbers this was not possible.

Independent variables negatively correlated with long-term survival included post-operative pulmonary vasodilator therapy, worse FC, higher mPAP, RAP and PVR and lower cardiac index. Our best-fit mPAP values of 36 mmHg for all-cause deaths and 38 mmHg for CTEPH direct deaths were similar to those reported in 2 smaller series where a post-operative mPAP of 34 mmHg and 37 mmHg correlated with poorer long-term outcome. [19, 26] In comparison, Skoro-Sajer and colleagues [23] did not find post-operative mPAP to be correlated with poorer outcome, but this may be due to the small sample size

in their study. Like mPAP, PVR has been reported as critical for post-PEA outcome and different thresholds suggested. [7, 12, 19, 23] Patients with a PVR above 500 dyne/sec/cm^{-5} immediately post PEA have a poorer peri-operative and 1 year survival. [7, 12] In comparison, data from Vienna suggests a PVR > 590 dyne/sec/cm^{-5} was correlated with poor longer-term outcome. [23] Our results show a slightly lower threshold with 416 dyne/sec/cm^{-5} for all cause mortality and 425 dyne/sec/cm^{-5} for CTEPH direct deaths.

Strengths and limitations

Our baseline and follow-up demographic and haemodynamic data are very similar to previously published retrospective and prospective series from both single and multicentres. [6, 7-31] This allows any conclusions from this current study to be transferrable to other centres outside the UK if the reassessment of patients post-PEA is similar. Our study has a number of strengths including the prospective data entry, a large sample size and careful systematic long-term follow-up by specialist PH physicians at designated PH Centres. We were also able to confirm the exact cause of death for all but one patient who died overseas, by obtaining death certificates for all patients. This allowed the adjudication of the cause of death by three independent observers. Our study also has a number of limitations. Although the data were entered prospectively it was not 100% complete, particularly for the patients in the early part of the cohort. For classification of residual PH ideally it would also be important to know whether the surgical clearance was completed at surgery, but at present there is no consensus about how this should be defined. Residual PH could be due to purely a small vessel arteriopathy or

mixed residual proximal disease and arteriopathy. This could contribute to a better description and prediction of those patients who may do worse or respond differently to treatment. Another factor that may alter the threshold for starting pulmonary vasodilator therapy post-PEA may be how well the right ventricle has re-modelled post-PEA. Interestingly, cardiac index was not found to independently predict long-term outcome or initiation of the pulmonary vasodilator therapy by multivariable analyses. Additionally, the methods for assessing right ventricular function by echocardiography have changed significantly over the study period making data analysis difficult.

Conclusion

Long-term survival post-PEA is excellent and the majority of patient deaths after the operative period were not due to right ventricular failure (CTEPH). Our data allow clinicians to better understand the natural history of CTEPH post-PEA and provides a description of patients at higher risk of long-term post-operative morbidity and mortality. Haemodynamics obtained 3-6 and/or 12 months after PEA allows stratification of patients at higher risk of dying from CTEPH and identifies a level of residual PH, which may help in the selection of patients who need to be monitored closely, and considered for other treatment options.

Acknowledgements

The authors wish to thank all the medical and nursing staff at each UK and Ireland PH centre that helped to manage this cohort of patients and specifically Prof. Nicholas Morrell, Marius Berman, Maureen Rootes, Iain

Armstrong, Paul Sephton, Jayne Jones, Jane Wilkinson, Sian Garrad, Sheila Forshaw, Rachel Crackett Dr Jay Sunthararlingham, Sally Reddecliffe, Adele Gallimore, Prof. Michael Gatzoulis, Carl Harries and Lisa Parfitt. We also acknowledge the helpful comments of the reviewers.

Funding sources

The National Institute of Health Research Cambridge Biomedical Research Centre provided research infrastructure. LS was supported by the Medical Research Council [Unit Programme number U105261167].

References

1. Cannon JE, Pepke-Zaba J. Is Distal Chronic Thromboembolic Pulmonary Hypertension Treatable with PAH Targeted Drugs? *Semin Respir Crit Care Med.* 2013;34(5):620-626.

2. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation.* 2011;124(18):1973-1981.

3. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest.* 1982;81(2):151-158.

4. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, Lang I, Madani MM, Ogino H, Pengo V, Mayer E. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol.* 2013;62(25 Suppl):D92-99.

5. Jenkins DP, Madani M, Mayer E, Kerr K, Kim N, Klepetko W, Morsolini M, Dartevelle P. Surgical treatment of chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2013;41(3):735-742.

6. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, Fedullo PF, Jamieson SW. Pulmonary Endarterectomy: Recent

Changes in a Single Institution's Experience of More Than 2,700 Patients. *Ann Thorac Surg.* 2012;94(1):97-103.

7. Mayer E, Jenkins D, Lindner J, D'Armini A, Kloek J, Meyns B, Ilkjaer LB, Klepetko W, Delcroix M, Lang I, Pepke-Zaba J, Simonneau G, Dartevelle P. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *J Thorac Cardiovasc Surg.* 2011;141(3):702-710.

8. Berman M, Gopalan D, Sharples L, Screaton N, Maccan C, Sheares K, Pepke-Zaba J, Dunning J, Tsui S, Jenkins DP. Right ventricular reverse remodeling after pulmonary endarterectomy: magnetic resonance imaging and clinical and right heart catheterization assessment. *Pulm Circ.* 2014;4(1):36-44.

9. Coronel ML, Chamorro N, Blanco I, Amado V, Del Pozo R, Pomar JL, Badia JR, Rovira I, Matute P, Argemí G, Castellà M, Barberà JA. Medical and Surgical Management for Chronic Thromboembolic Pulmonary Hypertension: A Single Center Experience. *Arch Bronconeumol.* 2014.

10. D'Armini AM, Zanotti G, Ghio S, Magrini G, Pozzi M, Scelsi L, Meloni G, Klersy C, Viganò M. Reverse right ventricular remodeling after pulmonary endarterectomy. *J Thorac Cardiovasc Surg.* 2007;133(1):162-168.

11. Freed DH, Thomson BM, Tsui SSL, Dunning JJ, Sheares KK, Pepke-Zaba J, Jenkins DP. Functional and haemodynamic outcome 1 year

after pulmonary thromboendarterectomy. *Eur J Cardiothorac Surg.* 2008;34(3):525-529; discussion 529-530.

12. Jamieson SW, Kapelanski DP, Sakakibara N, Manecke GR, Thistlethwaite PA, Kerr KM, Channick RN, Fedullo PF, Auger WR. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. *Ann Thorac Surg.* 2003;76(5):1457-1462; discussion 1462-1454.

13. Maliyasena VA, Hopkins PMA, Thomson BM, Dunning J, Wall DA, Ng BJ, McNeil KD, Mullany D, Kermeen FD. An Australian tertiary referral center experience of the management of chronic thromboembolic pulmonary hypertension. *Pulm Circ.* 2012;2(3):359-364.

14. Ogino H, Ando M, Matsuda H, Minatoya K, Sasaki H, Nakanishi N, Kyotani S, Imanaka H, Kitamura S. Japanese single-center experience of surgery for chronic thromboembolic pulmonary hypertension. *Ann Thorac Surg.* 2006;82(2):630-636.

15. Rubens FD, Bourke M, Hynes M, Nicholson D, Kotrec M, Boodhwani M, Ruel M, Dennie CJ, Mesana T. Surgery for chronic thromboembolic pulmonary hypertension--inclusive experience from a national referral center. *Ann Thorac Surg.* 2007;83(3):1075-1081.

16. Sato M, Ando M, Kaneko K, Higuchi Y, Kondo H, Akita K, Ishida M, Takagi Y. Respiratory and hemodynamic changes in patients with chronic thromboembolic pulmonary hypertension 1 year after pulmonary endarterectomy. *Ann Vasc Dis.* 2013;6(3):578-582.

17. Tscholl D, Langer F, Wendler O, Wilkens H, Georg T, Schäfers HJ. Pulmonary thromboendarterectomy--risk factors for early survival and

hemodynamic improvement. *Eur J Cardiothorac Surg.* 2001;19(6):771-776.

18. Yıldızeli B, Taş S, Yanartaş M, Kaymaz C, Mutlu B, Karakurt S, Altınay E, Eldem B, Ermerak NO, Batırel HF, Koçak T, Bekiroğlu N, Yüksel M, Sunar H. Pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension: an institutional experience. *Eur J Cardiothorac Surg.* 2013;44(3):e219-227; discussion e227.

19. Corsico AG, D'Armini AM, Cerveri I, Klersy C, Ansaldo E, Niniano R, Gatto E, Monterosso C, Morsolini M, Nicolardi S, Tramontin C, Pozzi E, Viganò M. Long-term outcome after pulmonary endarterectomy. *Am J Respir Crit Care Med.* 2008;178(4):419-424.

20. Mellemkjaer S, Ilkjaer LB, Klaaborg KE, Christiansen CL, Severinsen IK, Nielsen-Kudsk JE, Allermand H, Egeblad M, Kristensen BO. Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Ten years experience in Denmark. *Scand Cardiovasc J.* 2006;40(1):49-53.

21. Saouti N, Morshuis WJ, Heijmen RH, Snijder RJ. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a single institution experience. *Eur J Cardiothorac Surg.* 2009;35(6):947-952; discussion 952.

22. Schölzel B, Snijder R, Morshuis W, Saouti N, Plokker T, Post M. Clinical worsening after pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension. *Neth Heart J.* 2011;19(12):498-503.

23. Skoro-Sajer N, Marta G, Gerges C, Hlavin G, Nierlich P, Taghavi S, Sadushi-Kolici R, Klepetko W, Lang IM. Surgical specimens, haemodynamics and long-term outcomes after pulmonary endarterectomy. *Thorax.* 2014;69(2):116-122.

24. Matsuda H, Ogino H, Minatoya K, Sasaki H, Nakanishi N, Kyotani S, Kobayashi J, Yagihara T, Kitamura S. Long-term recovery of exercise ability after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *Ann Thorac Surg.* 2006;82(4):1338-1343; discussion 1343.

25. Bonderman D, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Dunkler D, Taghavi S, Klepetko W, Kneussl M, Lang IM. Predictors of outcome in chronic thromboembolic pulmonary hypertension. *Circulation.* 2007;115(16):2153-2158.

26. Ishida K, Masuda M, Tanabe N, Matsumiya G, Tatsumi K, Nakajima N. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg.* 2012;144(2):321-326.

27. Archibald CJ, Auger WR, Fedullo PF, Channick RN, Kerr KM, Jamieson SW, Kapelanski DP, Watt CN, Moser KM. Long-term outcome after pulmonary thromboendarterectomy. *Am J Respir Crit Care Med.* 1999;160(2):523-528.

28. Condliffe R, Kiely DG, Gibbs JSR, Corris PA, Peacock AJ, Jenkins DP, Hodgkins D, Goldsmith K, Hughes RJ, Sheares K, Tsui SSL, Armstrong IJ, Torpy C, Crackett R, Carlin CM, Das C, Coghlan JG, Pepke-Zaba J. Improved outcomes in medically and surgically treated

chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2008;177(10):1122-1127.

29. Freed DH, Thomson BM, Berman M, Tsui SSL, Dunning J, Sheares KK, Pepke-Zaba J, Jenkins DP. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. *J Thorac Cardiovasc Surg.* 2011;141(2):383-387.

30. van der Plas MN, Surie S, Reesink HJ, van Steenwijk RP, Kloek JJ, Bresser P.

Longitudinal follow-up of six-minute walk distance after pulmonary endarterectomy. *Ann Thorac Surg.* 2011;91(4):1094-1099.

31. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jaïs X, Ambroz D, Treacy C, Morsolini M, Jenkins D, Lindner J, Dartevelle P, Mayer E and Simonneau G. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension (CTEPH): Results from an international prospective registry. Circulation. 2016 Jan 29. pii: CIRCULATIONAHA.115.016522.

32. Dartevelle P, Fadel E, Mussot S, Chapelier A, Hervé P, de Perrot M, Cerrina J, Ladurie FL, Lehouerou D, Humbert M, Sitbon O, Simonneau G. Chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2004;23(4):637-648.

33. Moser KM, Braunwald NS. Successful surgical intervention in severe chronic thromboembolic pulmonary hypertension. *Chest.* 1973;64(1):29-35.

34. Thistlethwaite PA, Kaneko K, Madani MM, Jamieson SW. Technique and outcomes of pulmonary endarterectomy surgery. *Ann Thorac Cardiovasc Surg.* 2008;14(5):274-282.

35. Ghofrani H-A, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C, Group C-S. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med.* 2013;369(4):319-329.

36. Taboada D, Pepke-Zaba J, Jenkins DP, Berman M, Treacy CM, Cannon JE, Toshner M, Dunning JJ, Ng C, Tsui SS, Sheares KK. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. *Eur Respir J.* 2014.

37. Thomson B, Tsui SSL, Dunning J, Goodwin A, Vuylsteke A, Latimer R, Pepke-Zaba J, Jenkins DP. Pulmonary endarterectomy is possible and effective without the use of complete circulatory arrest--the UK experience in over 150 patients. *Eur J Cardiothorac Surg.* 2008;33(2):157-163.

38. Vuylsteke A, Sharples L, Charman G, Kneeshaw J, Tsui S, Dunning J, Wheaton E, Klein A, Arrowsmith J, Hall R, Jenkins D. Circulatory arrest versus cerebral perfusion during pulmonary endarterectomy surgery (PEACOG): a randomised controlled trial. *Lancet.* 2011;378(9800):1379-1387.

39. Thistlethwaite PA, Mo M, Madani MM, Deutsch R, Blanchard D, Kapelanski DP, Jamieson SW. Operative classification of

thromboembolic disease determines outcome after pulmonary endarterectomy. *J Thorac Cardiovasc Surg.* 2002;124(6):1203-1211.

40. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Annals of Statistics.*1988;16:1141-54.

41. Grambsch PM and Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81(3):515-26

42 Klein JP and Wu JT. Discretizing a Continuous Covariate in Survival Studies. *Handbook of Statistics* 2004; 23:27-42.

43. Rahnavardi M, Yan TD, Cao C, Vallely MP, Bannon PG, Wilson MK. Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension : a systematic review. *Ann Thorac Cardiovasc Surg.* 2011;17(5):435-445.

44. Lewczuk J, Piszko P, Jagas J, Porada A, Wójciak S, Sobkowicz B, Wrabec K. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest.* 2001;119(3):818-823.

45. Jansa P, Ghofrani H-A, Hoeper MM, Kim NH, Meyer E, Neurohr C, Simonneau G, Fritsch A, Davie N, Wilkins MR. Comparison of haemodynamic parameters in patients with inoperable and persistent/recurrent chronic thromboembolic pulmonary hypertension in the Phase III CHEST-1 study. *Eur Heart J*. 2013; 34 (Abstract Supplement), 187:1066.

Tables

	Pre-operative	Post-operative	p-value
Age (years)	57 ± 15		
Sex (Male: Female %)	53:47		
BMI kg/m^2	28.7 ± 6.3		
FC 1/2/3/4 %	0/9/68/23	38/47/15/0	< 0.0001*
mPAP (mmHg)	47 ± 11	27 ± 10	< 0.0001*
PVR (dyne/sec/cm^{-5})	830 ± 382	317 ± 239	< 0.0001*
6MWD (m)	260 ± 126	353 ± 118	< 0.0001*
TLco (% predicted)	67		
Pulmonary vasodilator therapy (%)	64		
Mechanical ventilation length of time median (mean±SD) (days)	1 (2.5 ± 4)		
ICU length of stay median (mean±SD) (days)	3 (7 ± 9)		
Hospital length of stay median (mean±SD) (days)	16 (20 ± 14)		

Table 1. Baseline and post-surgery patient characteristics. Baseline (n = 880) and post-operative characteristics (n = 748). Post-operative results are from 3-6 month post-PEA review. Values are mean ± standard deviation. FC - WHO functional class, mPAP - mean pulmonary artery pressure, PVR - pulmonary vascular resistance, 6MWD - six-minute walk distance, TLco - transfer co-efficient of the lung for carbon monoxide. * vs. pre-operative values from paired t-tests (mPAP, PVR, 6MWD) and Wilcoxon signed rank test (for difference between pre-operative and post-operative FC).

Variables		Hazard Ratio	95% CI		p-value	N*
Functional class (baseline)	1,2				0.0002	116
	3	3.74	0.89	15.73		
	4	7.77	1.80	33.54		
Six minute walk (baseline)		0.65	0.52	0.80	<.0001	101
mPAP (baseline)	Linear effect	1.44	1.12	1.84	0.0138	113
	Quadratic effect	0.86	0.74	0.99		
RAP (baseline)		1.29	1.12	1.50	0.0007	103
Cardiac index (baseline)		0.79	0.67	0.94	0.0070	111
PVR (baseline)	Linear effect	1.27	1.09	1.48	0.0008	112
	Quadratic effect	0.90	0.84	0.96		
Functional class (over time)	1				<.0001	
	2	3.94	1.73	8.97		95
	>=3	22.84	9.83	53.05		
Six minute walk (over time)		0.52	0.40	0.68	<.0001	88
mPAP (over time)	Linear effect	25.77	11.98	55.41	<.0001	92
	Quadratic effect	0.52	0.41	0.67		
RAP (over time)		1.84	1.48	2.27	<.0001	91
Cardiac index (over time)		0.81	0.65	1.02	0.067	92
PVR (over time)	Linear effect	1.87	1.46	2.39	<.0001	92
	Quadratic effect	0.75	0.69	0.83		
TLco (over time)		0.44	0.33	0.60	0.0142	66

Table 2 Multivariable analyses for factors correlated with treatment initiation. These were adjusted for the following factors: gender, age, baseline BMI, baseline history of atrial flutter or fibrillation or COPD, bridging

treatment pre-surgery and intraoperative classification of disease**.** All continuous variables were standardized (cardiac index: x-2.5/0.5, mPAP: x-25/10, PVR: x-250/200). Quadratic terms for continuous variables are included if the formal tests on non-linearity are significant at 5% level. *N is the number of events (pulmonary vasodilator therapy initiation) available for analyses.

Variables		Hazard Ratio	95% CI		p-value	N*
Functional class (over time)	1				<.0001	52
	2	6.37	2.23	18.26		
	>=3	12.88	4.11	40.41		
Six minute walk (over time)		0.48	0.35	0.68	<.0001	48
mPAP (over time, continuous)		1.57	1.20	2.04	0.0008	49
mPAP (over time, categorized)	<25				0.0003**	49
	[25,30)	0.60	0.22	1.65		
	[30,38)	1.57	0.66	3.75		
	38+	3.85	1.87	7.92		
RAP (over time)		1.95	1.46	2.60	<.0001	49
Cardiac index(over time, continuous)		0.82	0.61	1.12	0.2149	48
Cardiac index (over time, categorized)	<2.16				0.0246**	48
	>=2.16	0.51	0.28	0.92		
PVR (over time, continuous)		1.62	1.29	2.03	<.0001	47
PVR (over time, categorized)	<250				<.0001**	47
	[250,425)	0.62	0.24	1.61		
	425+	4.69	2.25	9.78		
TLco (over time)		0.71	0.43	1.15	0.1615	24
Pulmonary vasodilator therapy initiated	YES	2.59	1.48	4.53	0.0009	68
ECMO	YES	2.91	0.97	8.69	0.0562	68

Table 3 Multivariable analyses for long-term mortality. Factors were adjusted for gender, age, baseline BMI, prior history of malignancy or myeloproliferative disorder and hospital length of stay. All continuous variables were standardized (see Table 2 legend). *N is the number of events (death) available for analyses. ** These p-values are not corrected for bias induced by selecting the largest likelihood ratio test statistics and cannot be used for inference. [41]

Figures

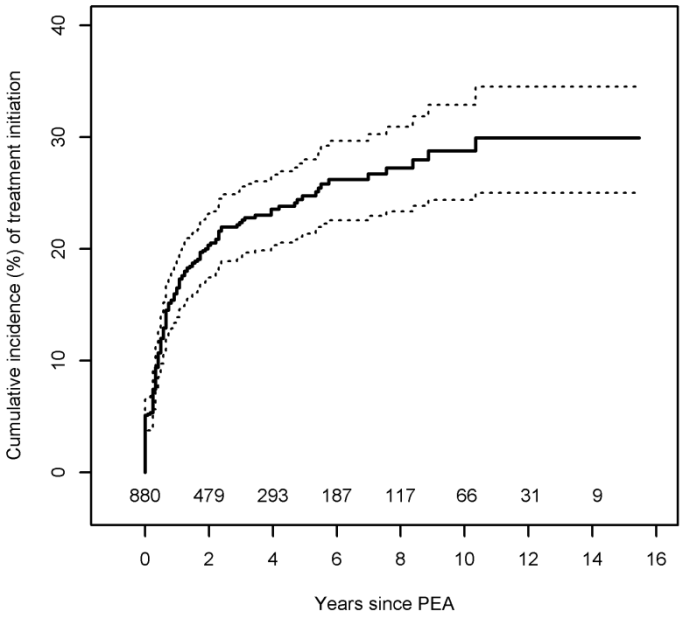

Figure 1. Cumulative incidence (%) of pulmonary vasodilator therapy initiation after pulmonary endarterectomy. Number of patients at risk of treatment initiation over follow-up as shown.

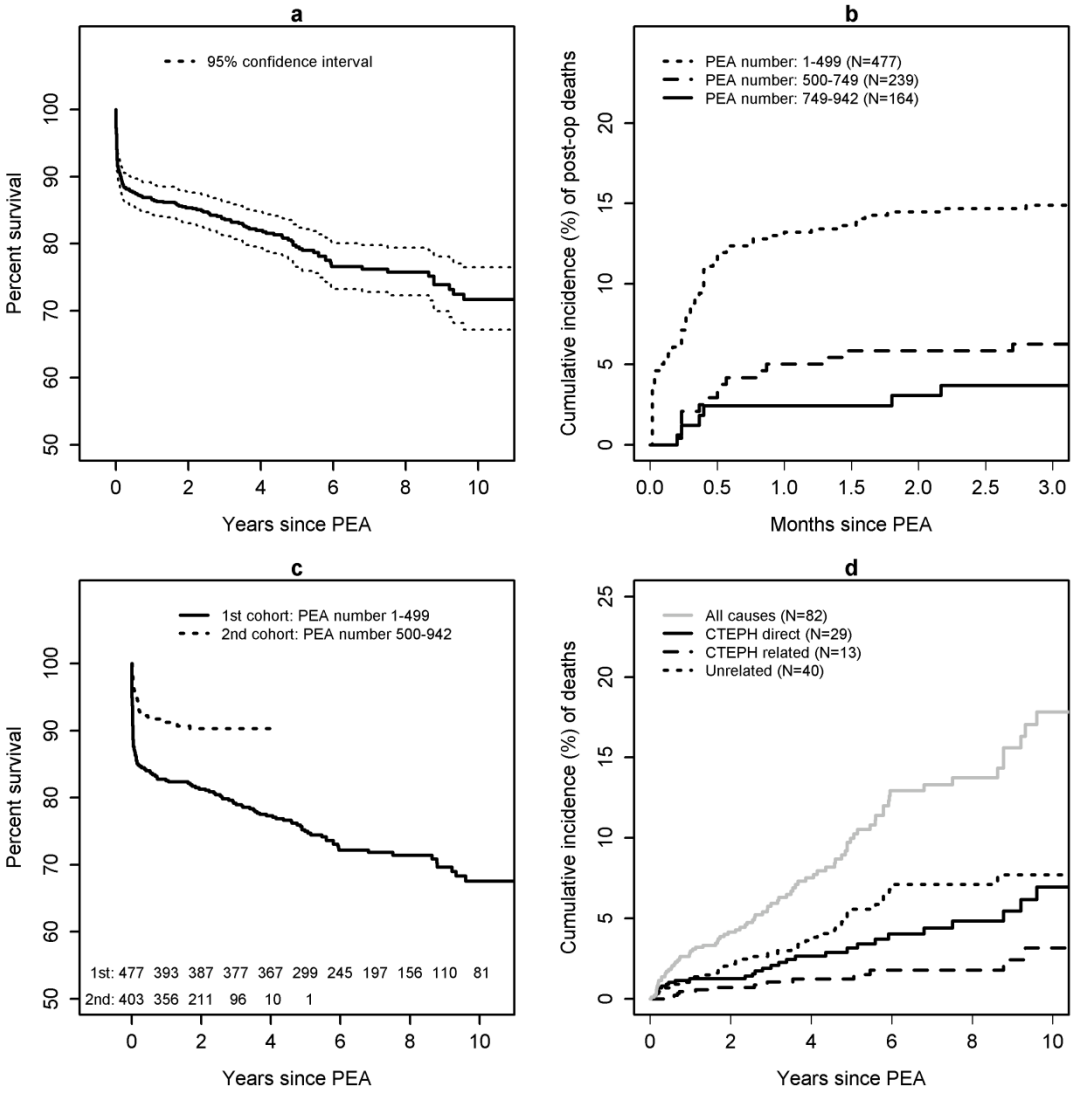

Figure 2 Survival and classification of causes of death for PEA cohort.

a) Kaplan-Meier curve showing cohort survival. b) Cumulative incidence of post-operative deaths improves with centre experience. PEA number is consecutive PEA operations including indications other than CTEPH. N= number of PEA operations for CTEPH. c) Kaplan-Meier curve comparing survival of 1st vs. 2nd half of cohort. d) Cumulative incidence of causes of death (see methods for classification) for patients surviving post-operative period. The number of patients at risk over follow-up as shown bottom of a) and c).

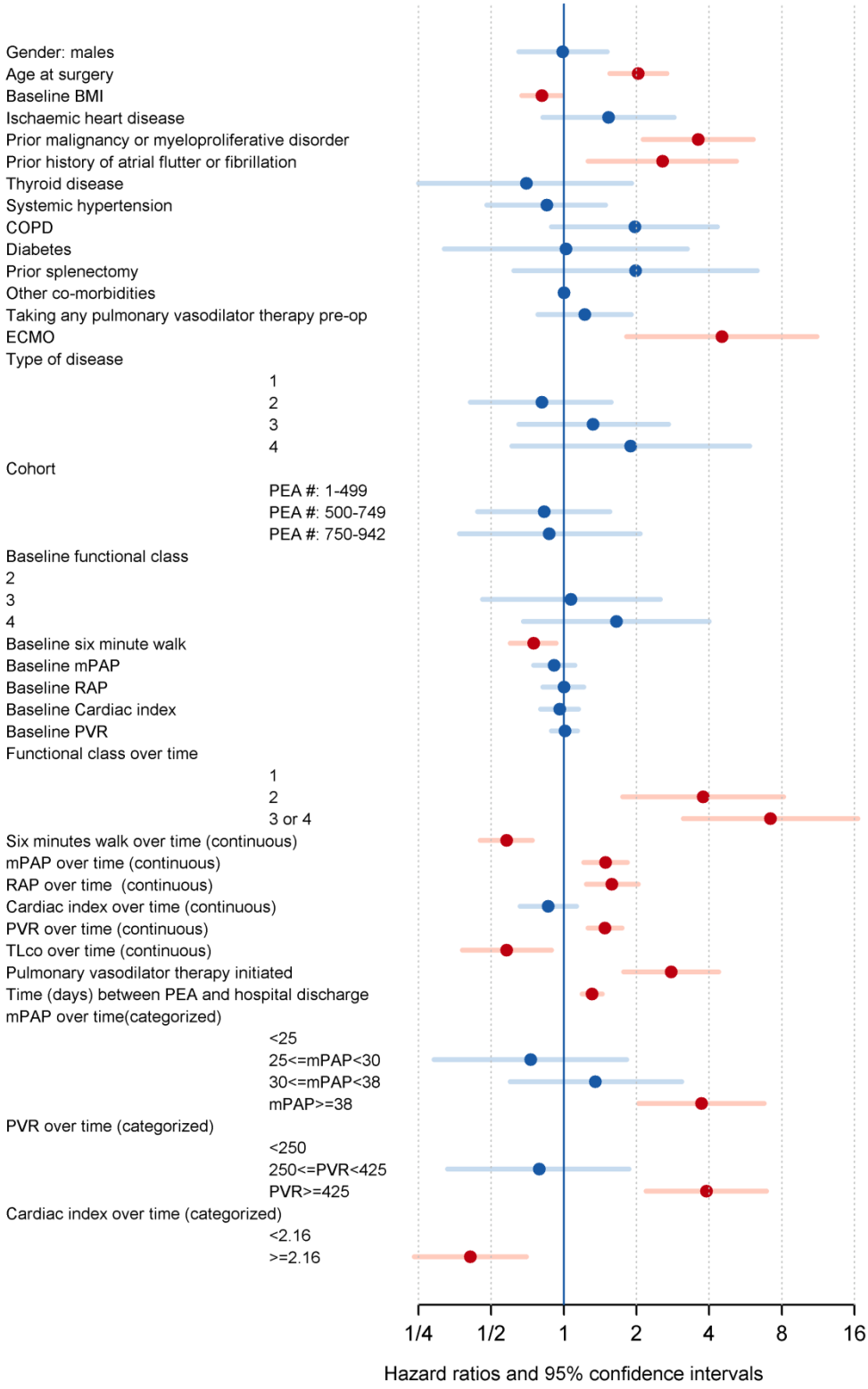

Figure 3. Variables correlated with long-term mortality by univariable analyses. All continuous variables were standardized (see Table 2 legend).

Red circles/bars define significant factors ($p<0.05$) and blue the non-significant factors.