Life expectancy after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a Swedish single-center study

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Abstract
Pulmonary endarterectomy is the guideline recommended treatment for chronic thromboembolic pulmonary hypertension, in addition to life-long anticoagulation therapy. The aim was to analyze long-term relative survival after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. We included all patients who underwent pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension at Karolinska University Hospital between 1997 and 2018 (n = 100). We obtained baseline characteristics and vital status from patient charts and national health-data registers. The expected survival from the general Swedish population matched by age, sex, and year of surgery was obtained from the Human Mortality Database. The relative survival was used as an estimate of cause-specific mortality. The mean age of the patients was 62 years and 39% were women. Most patients were severely symptomatic (95% in New York Heart Association functional class III–IV), and mean pre-operative systolic/diastolic (mean) pulmonary artery pressure was 78/27 (45) mmHg. The mean and maximum follow-up time was 7.2 and 22.1 years, respectively. Early (30-day) mortality was 7%. The 15-year observed, expected, and relative survival was 55% (95% confidence interval, 40%–68%), 71%, and 77% (95% confidence interval, 56%–95%), respectively. The 15-year relative survival conditional on 30-day survival was 83% (95% confidence interval, 60%–100%). Although the life expectancy following pulmonary endarterectomy was shorter compared to the general population, the difference was small in those who survived the operation and the early postoperative period. Patients with chronic thromboembolic pulmonary hypertension who are surgical candidates should undergo pulmonary endarterectomy to improve prognosis.

Keywords
pulmonary endarterectomy, chronic thromboembolic pulmonary hypertension, survival, life expectancy

Introduction
Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare medical condition affecting about 0.5%–4% of patients surviving pulmonary embolism (PE). In Sweden, the four-year mortality for inoperable CTEPH was 55%–60% according to the Annual Report of 2018 from the Swedish Arterial Pulmonary Hypertension Registry. Patients with coagulopathies are overrepresented in the group of patients diagnosed with CTEPH and many of the patients have a history of venous thromboembolism. The exact cellular mechanisms leading from acute PE to CTEPH are still unclear, but vascular remodeling with intimal hyperplasia in the pulmonary arteries serves an important role. Mechanical obstruction of the
pulmonary arteries with unresorbed thrombi leads to fibrosis and stenosis, with complete or partial occlusions of the pulmonary arteries. Via the bronchial circulation, the pulmonary vascular bed receives circulating blood to the non-obstructed parts of the lungs. According to Dorfmüller et al., this bronchopulmonary venous shunting may contribute to microvascular changes and even more vasoconstriction.9 This results in an increase in pulmonary vascular resistance and elevated blood pressure in the pulmonary arteries causing right heart failure. Patients seek care for vague symptoms such as dyspnea and fatigue. Different imaging tools are needed in order to diagnose CTEPH. Echocardiography is commonly used as the first screening tool to study pulmonary artery pressures (PAPs) and signs of right heart failure. Lung perfusion defects are evaluated with scintigraphy, and right heart catheterization is used to verify and precisely measure PAPs, pulmonary vascular resistance, and cardiac output. Pulmonary angiography is then used to evaluate the operability with respect to central or distal pathology in the vessels.10 There are three main treatment modalities for CTEPH. Pulmonary endarterectomy (PEA) is the primary treatment of operable CTEPH.11 Targeted therapy with riociguat offers inoperable patients or patients with residual or recurrent pulmonary hypertension (PH) after PEA relief in symptoms with higher exercise capacity and improved hemodynamics.12,13 During the last decade, balloon pulmonary angioplasty (BPA) has evolved as a possible treatment for inoperable CTEPH or for patients with residual or recurrent PH after PEA. BPA has been shown to result in a reduction of PAP.14 As a complement to these therapeutic options, pharmacological treatment with life-long anticoagulation is of great importance. PEA is performed via median sternotomy using cardiopulmonary bypass with deep hypothermia and circulatory arrest. The endarterectomies are then performed through incisions in the pulmonary arteries.15–17 PEA is the only curative treatment for CTEPH, but little is known about survival in this patient group compared to the general population. The aim of this study was to analyze long-term relative survival in patients undergoing PEA surgery for CTEPH compared to the general population.

Methods

Study design

This observational cohort study was approved by the regional Human Ethics Committee in Stockholm, Sweden (2018/1296-31). No informed consent was required. We included all patients who underwent PEA for CTEPH at Karolinska University Hospital between 1997 and 2018 (n = 100). We obtained baseline characteristics and vital status from patient charts and national health data registries. Surgery was performed according to established techniques through a median sternotomy, and a complete bilateral endarterectomy was done during one or more episodes of circulatory arrest at a body temperature of 18°C.

The expected survival from the general Swedish population matched by age, sex, and year of surgery was obtained from the Human Mortality Database (www.mortality.org). In the Human Mortality Database, researchers can find detailed open access information about population and mortality in 41 countries. Information about birth rates, population size, exposure to risk, death rates, and life tables is also available.

Statistical methods

Baseline characteristics were described with frequencies and percentages for categorical variables and means and standard deviations (SDs) for continuous variables. Person-time in days was calculated from the date of surgery until the date of death or end of follow-up (April 1, 2019). The Kaplan–Meier method was used to calculate cumulative survival. The expected survival from the general population in Sweden matched by age, sex, and year of surgery was obtained from the Human Mortality Database. The expected and observed survival curves were constructed with the strs18 Stata command. Data management and statistical analyses were performed using Stata 16.0 (Stata Corp LP, College Station, TX, USA) and included the use of the strs18 program.

Results

A total of 100 patients were included (Fig. 1). The mean age of the patients was 62 (range 23–81) years and 39% were women. The mean body mass index for the patients was 26.6 (SD 5.0), 19% of the patients had concomitant chronic obstructive pulmonary disease, 5% had suffered a prior stroke, and 73% of the patients had normal kidney function. Most patients were severely symptomatic.
(95% in New York Heart Association functional class III–IV), and preoperative mean systolic/diastolic PAP was 78/27 mmHg. Mean PAP in the patients was 45 mmHg (SD 11). The majority, 86% of the patients, had normal left ventricular ejection fraction and none of the patients had severely depressed left ventricular ejection fraction (Table 1).

The mean and maximum follow-up time was 7.2 and 22.1 years, respectively. Early (30-day) mortality was 7%.

As shown in Table 2, at five years, the observed survival was 80% (95% confidence interval (CI), 70%–87%), whereas the expected five-year survival in a sex, age, and year-of-surgery matched population was 92%. The relative survival at five years was 87% (95% CI, 77%–94%). Conditional on 30-day survival, the observed, expected, and relative survival was 86% (95% CI, 77%–92%), 92%, and 94% (95% CI, 83%–100%), respectively.

At 10 years, the observed survival was 69% (95% CI, 57%–78%), the expected survival was 82%, and the relative survival was 84% (95% CI, 69%–96%). Conditional on 30-day survival, the observed, expected, and relative survival at 10 years was 74% (95% CI, 61%–83%), 82%, and 91% (95% CI, 75%–100%), respectively.

The 15-year observed, expected, and relative survival was 55% (95% CI, 40%–68%), 71%, and 77% (95% CI, 56%–95%), respectively. Conditional on 30-day survival, observed, expected, and relative survival was 59% (95% CI, 43%–72%), 71%, and 83% (95% CI, 60%–100%), respectively.

The Kaplan–Meier estimated survival is shown in Fig. 2, and the observed and expected survival is shown in Fig. 3. As shown in Fig. 4, the female relative survival was 53% (95% CI, 32%–73%) for the cohort, whereas for men 76% (54%–94%).

### Table 1. Baseline characteristics in 100 patients who underwent pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension in Stockholm between 1997 and 2018.

| Variable                                      | Total study population (n = 100) |
|-----------------------------------------------|---------------------------------|
| N                                             | 100                             |
| Age, years, mean (SD), median (Q1/Q3)         | 62 (13), 64 (54/72)             |
| Men                                           | 61 (61%)                        |
| Women                                         | 39 (39%)                        |
| Body mass index, kg/m², mean (SD), median (Q1/Q3) | 26.9 (5.0), 25.7 (23.5/29.1)    |
| Hypertension                                  | 8 (8%)                          |
| Atrial fibrillation                           | 19 (19%)                        |
| Diabetes                                      | 1 (1%)                          |
| Chronic obstructive pulmonary disease         | 19 (19%)                        |
| Prior PCI                                     | 2 (2%)                          |
| Peripheral artery disease                     | 0                               |
| Prior stroke                                  | 5 (5%)                          |
| eGFR                                          |                                 |
| >60 mL/min/1.73 m²                            | 73 (73%)                        |
| <60 mL/min/1.73 m²                            | 27 (27%)                        |
| Left ventricular ejection fraction            |                                 |
| >50%                                          | 86 (86%)                        |
| 30%–50%                                       | 14 (14%)                        |
| <30%                                          | 0                               |
| NYHA class                                    |                                 |
| I                                             | 0                               |
| II                                            | 5 (5%)                          |
| III                                           | 76 (76%)                        |
| IV                                            | 19 (19%)                        |
| Systolic PAP, mmHg, mean (SD), median (Q1/Q3) | 78 (19), 77 (66/89)             |
| Diastolic PAP, mmHg, mean (SD), median (Q1/Q3) | 27 (9.3), 28 (22/33)            |
| Mean PAP, mmHg, mean (SD), median (Q1/Q3)     | 45 (11), 47 (39/52)             |

Note: Numbers are n (%) unless otherwise noted. SD: standard deviation; Q1/Q3: 25th/75th percentile; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PCI: percutaneous coronary intervention.
Discussion

The main finding of our study was that life expectancy following PEA was shorter compared to the general population, but the difference was relatively small. In patients who survived the operation and early postoperative phase, survival at 15 years was 59% compared to 71% in the matched general population, and the relative survival was 83% (95% CI, 60%–100%). Of note, the relative survival was worse in women compared to men.

In comparison, the prognosis for inoperable CTEPH is discouraging with a 3-year survival of 70% according to the European CTEPH registry, a 5-year survival in Sweden of about 50%, and a 10-year survival at only 40% in a Korean population. Similar results were published by Quader et al., who reported a five-year survival between 53% and 59% in inoperable patients.

Patients undergoing PEA at dedicated high-volume centers have excellent long-term survival with 5-year survival between 79% and 82% and 10-year survival between 72% and 75%. These PEA populations have not been compared to a general age, sex, and year of surgery matched population, and therefore, our study complements prior findings and adds information about the prognosis after PEA in patients with CTEPH.

Delcroix et al. performed a multicenter, prospective registry study with data obtained from the CTEPH registry from 27 centers in Europe and Canada. They included newly diagnosed CTEPH patients who underwent PEA between 2007 and 2009 (n = 404) and found a three-year survival of 89% and an in-hospital mortality rate of 4.4%. Mean age for the patients at the time of surgery was 60 years.

Results from the world’s largest PEA cohort from the University of California, San Diego, by Madani et al., demonstrated a 10-year survival of 75% for patients who underwent PEA surgery. In their study, 1410 patients were included between 1999 and 2010, and the mean age at time of surgery was 52 years.

Papworth Hospital in Cambridge is the national center for PEA in the UK. Cannon et al. reported a 10-year survival of 72% for 880 consecutive patients who underwent PEA between 1997 and 2012. Mean age at the time of surgery was 57 years. Conditional on three-month survival, the five-year survival at Papworth Hospital was 92.5% for a cohort who underwent PEA between 1997 and 2006. In comparison, the five-year survival conditional on 30-day survival was 86% in our study.

Korsholm et al. at Aarhus University Hospital, the national center for PEA in Denmark, recently reported excellent results in 239 patients who underwent PEA between 1994 and 2016. In their study, the 10-year survival rate was 62%. The in-hospital mortality was 8.4% for the entire cohort and interestingly, it decreased from 22.6% in the early era to 4.3% in the later part of the study period. The majority of patients had an improvement in functional class and 6-min walk test postoperatively. Median follow-up time was 4.4 years, and the mean age at the time of surgery was 60 years. Based on available data, the patient baseline characteristics in the Danish study appear similar to the patient population that were operated at Karolinska University Hospital.

Interestingly, we found that women had worse relative survival compared to men. This observation needs further investigation, and the reason for this trend is unclear.

| Table 2. Observed, expected, and relative survival in patients who underwent pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension in Stockholm between 1997 and 2018. |
|---------------------------------------------------------------|
| Number of patients | Observed mean survival (95% CI), % | Expected mean survival, % | Relative survival (95% CI), % |
| Total study population | 100 | 53 (40–64) | 80 | 66 (51–80) |
| At 1 year | 89 | 91 (83–95) | 99 | 92 (85–97) |
| At 5 years | 64 | 80 (70–87) | 92 | 87 (77–94) |
| At 10 years | 29 | 69 (57–78) | 82 | 84 (69–96) |
| At 15 years | 8 | 55 (40–68) | 71 | 77 (56–95) |
| At 19 years | 4 | 40 (20–59) | 60 | 67 (34–100) |
| Sex | | | | |
| Women | 39 | 46 (28–63) | 87 | 53 (32–73) |
| Men | 61 | 58 (41–71) | 76 | 76 (54–94) |
| Conditional on 30-day survival | 93 | 59 (46–70) | 80 | 74 (57–87) |
| At 1 year | 89 | 98 (92–100) | 99 | 99 (93–100) |
| At 5 years | 64 | 86 (77–92) | 92 | 94 (83–100) |
| At 10 years | 29 | 74 (61–83) | 82 | 91 (75–100) |
| At 15 years | 8 | 59 (43–72) | 71 | 83 (60–100) |
| At 19 years | 4 | 43 (21–63) | 60 | 72 (36–100) |

CI: confidence interval.
Possible explanations could be gender differences related to severity of disease at the time of diagnosis or higher burden of comorbidity at the time of surgery. It has been shown that preoperative higher mean PAP confers higher mortality and worse prognosis. It is also possible that females are more prone to peripheral disease and therefore have worse surgical outcome with, for example, signs of residual elevation in mean PAP. Additionally, mean expected survival in females in Sweden is generally high with 84.25 years, according to Statistics Sweden, which also impacts relative survival. This finding warrants further investigations, preferably in a larger patient cohort to better understand possible gender differences. A recent study from Barco et al. from the CTEPH registry demonstrated better long-term survival for women than for men over a three-year period (83% for men and 93% for women).
females vs. 79.3% for men). Their study was limited by a small study population and only reported a single-center experience. Their cohort also stretches over a long period of time, 11 years. During this time, perioperative management of the patients has improved and treatment with specific pulmonary hypertension drugs has been refined.

**Study limitations**

Our findings should be interpreted in light of the fact that patients were included from a single center, and the findings may therefore not be generalizable to other centers or countries. It is possible that changes in diagnosis, referral, and care of patients with CTEPH during the study period could have affected our results. A limitation of our study is the lack of information regarding post-PEA treatment, such as targeted medication and/or BPA.

**Conclusions**

Although the life expectancy following PEA was shorter compared to the general population, the difference was small. Our results suggest worse relative survival in women compared to men, a finding that needs further investigation. Given the dismal prognosis without effective treatment, patients with CTEPH who are surgical candidates should undergo PEA to improve survival.

**Conflict of interest**

The author(s) declare that there is no conflict of interest.

**Funding**

This work was supported by the Swedish Heart-Lung Foundation (grant numbers 20160522, 20160525, and 20180400 to U.S.), Ake Wiberg Foundation (grant number M18-0016 to U.S.), Karolinska Institutet Foundations and Funds (grant number 20160522, 20160525, and 20180400 to U.S.), and grants provided by Region Stockholm (ALF project, grant number 20180114 to U.S.).

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