Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

LONG-TERM FOLLOW-UP AFTER SURGERY FOR CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Janica Kallonen

Karolinska Institutet

Stockholm 2023

Published by Karolinska Institutet.

Printed by Universitetsservice US-AB, 2023

ISBN 978-91-8016-950-9

Cover illustration: “The Convalescent” by Helene Schjerfbeck 1888. Photo: Finnish National Gallery/Yehia Eweis

Long-term follow-up after surgery for chronic thromboembolic pulmonary hypertension

Thesis for doctoral degree (Ph.D.)

By

Janica Kallonen

The thesis will be defended in public at Rolf Luft Auditorium, L1:00, Anna Stecksens gata 53, Karolinska Institutet, Stockholm, on May 5, 2023, at 09:00.

Principal Supervisor:
Professor Ulrik Sartipy
Karolinska Institutet
Department of Molecular Medicine and Surgery

Co-supervisor:
Associate Professor Matthias Corbascio
Karolinska Institutet
Department of Molecular Medicine and Surgery

Opponent:
Professor Stefan Söderberg
Umeå University
Department of Public Health and Clinical Medicine

Examination Board:
Associate Professor Karolina Szummer
Karolinska Institutet
Department of Medicine

Associate Professor Aristomenis Manouras
Karolinska Institutet
Department of Medicine

Associate Professor Shahab Nozohoor
Lund University
Department of Clinical Sciences

Popular science summary of the thesis

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease caused by unresolved blood clots in the arteries of the lungs. Scar tissue forms, causing narrowings in these arteries. This leads to elevated blood pressure in the circulation of the lungs and puts a strain on the right heart. Right heart failure develops and can lead to death. The symptoms of CTEPH are shortness of breath and fatigue. Many patients with CTEPH have a previous history of blood clots in the legs or lungs. CTEPH can be treated with open heart surgery, an operation known as pulmonary endarterectomy. During this operation the arteries of the lungs are cleared of scar tissue making it easier for blood to flow to the lungs, thereby reducing the strain on the right heart. Many patients improve greatly after surgery, which is the treatment of choice for all patients who are good surgical candidates. All patients with CTEPH must remain on blood thinners lifelong to avoid new blood clots. Other treatment options that offer symptomatic relief are medical therapy or a catheter-based procedure.

This thesis consists of four studies in which we investigated the long-term outcomes after surgery for CTEPH. In *Study I,* we investigated whether survival after surgery for CTEPH is comparable to that of the general population in Sweden. We found that life expectancy after surgery for CTEPH was slightly shorter than that in the general population. However, when patients who died within 30 days of surgery were excluded from the analyses, the life expectancy was very close to that of the general population.

In *Study II* we sought to determine if there are any sex-related differences in survival after surgery for CTEPH. Women had a higher risk of dying early after surgery than men. After adjustment for baseline characteristics, there was no significant difference in survival between the sexes. However, the survival of men was close to expected, while women deviated more from expected survival.

Study III investigated whether measurement of blood pressure in the arteries of the lungs early after surgery for CTEPH can predict long-term survival. After adjusting for baseline characteristics, we found that patients with higher blood pressure in the arteries of the lungs had worse long-term survival than those with lower blood pressure in these arteries in the early postoperative period.

In *Study IV,* we investigated quality of life after surgery for CTEPH. The study participants had a near-normal quality of life when compared with an age-matched Swedish population. All the study participants were able to live at home, care for most personal needs, and most were able to continue with their normal activities and work.

In conclusion, we suggest that all patients with CTEPH should be referred to an expert centre and evaluated for surgery to improve their survival and quality of life.

Abstract

Background

Pulmonary endarterectomy (PEA) is the treatment recommended for all operable patients with chronic thromboembolic pulmonary hypertension (CTEPH). The aim of this thesis was to evaluate long-term survival, quality of life (QoL) and functional status in patients with CTEPH who have undergone PEA.

Methods and results

Study I Survival after PEA was compared with that in the Swedish general population. We included all patients who underwent PEA at Karolinska University Hospital between 1997 and 2018 (N=100). Information on expected survival in the general Swedish population matched for age, sex, and year of surgery was obtained from the Human Mortality Database. The 10-year observed, expected, and relative survival rates were, respectively 69% (95% confidence interval [CI], 57–78), 82%, and 84% (95% CI 69–96).

Study II Sex-specific survival after PEA for CTEPH was investigated. All patients who underwent PEA at two Scandinavian centres between 1992 and 2020 were included (N=444; 59% male, 41% female). Data on expected survival in the general population matched for age, sex, and year of surgery were obtained from the Human Mortality Database. Propensity scores and weighting were used to account for differences at baseline. Flexible parametric survival models were used. Unadjusted 30-day mortality was 4.2% in men and 9.8% in women (p=0.020). In weighted analyses, long-term survival did not differ significantly between men and women (hazard ratio: 1.36; 95% CI 0.89–2.06). Relative survival at 15 years conditional on 30-day survival was 94% (95% CI 79–107) in men and 75% (95% CI 59–88) in women.

Study III The association between residual pulmonary hypertension after PEA and long-term survival was investigated. All patients who underwent PEA at two Scandinavian centres between 1992 and 2020 (N=444) were included. Residual pulmonary hypertension was defined as an early postoperative mean pulmonary artery pressure of ≥30 mmHg. After weighting, there was a significant association between residual pulmonary hypertension and all-cause mortality (hazard ratio 2.49; 95% CI 1.60–3.87), and the absolute survival difference between the groups was -22% (95% CI -32 to -12) at 10 years and -32% (95% CI -47 to -18) at 20 years.

Study IV QoL and functional status were investigated in a cross-sectional manner. All patients who underwent PEA for CTEPH at Karolinska University Hospital between 1992 and 2020 were enrolled. Data were obtained from patient charts and national health data registers as well as from RAND-36 questionnaires and telephone interviews. The RAND-36

scores were slightly lower in the patients who underwent PEA for CTEPH than in the Swedish age-matched reference population in all domains except for bodily pain. All patients, in whom Karnofsky Performance Status was assessed (N=42), were able to live at home and care for most of their personal needs and 74% were able to carry on normal activities. The mean postoperative scores measured by the Cambridge Pulmonary Hypertension Outcome Review were low.

Conclusions

Life expectancy following PEA was shorter than that in the general population, but the difference was small.

There was a sex-specific difference in the prognosis after PEA in that women had a higher early mortality rate. However, after adjustment for differences in baseline characteristics, there was no significant sex-related difference in long-term survival despite women deviating more from expected survival than men.

Patients with early postoperative residual pulmonary hypertension had worse long-term survival after PEA.

QoL after PEA was close to that expected in a reference population, and functional status improved slightly when assessed late after PEA. These findings suggest that many patients enjoy satisfactory QoL and high functional status late after PEA.

List of scientific papers

I. **Kallonen J**, Glaser N, Bredin F, Corbascio M, Sartipy U. Life expectancy after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a Swedish single-center study. *Pulm Circ* 2020; 10(2) 1–7

II. **Kallonen J**, Korsholm K, Bredin F, Corbascio M, Andersen MJ, Ilkjær LB, Mellemkjær S, Sartipy U. Sex and survival following pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a Scandinavian observational cohort study. *Pulm Circ* 2021; 11(4) 1–9

III. **Kallonen J**, Korsholm K, Bredin F, Corbascio M, Jønsson Andersen M, Ilkjær LB, Mellemkjær S, Sartipy U. Association of residual pulmonary hypertension with survival after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *Pulm Circ* 2022; 12: e12093.

IV. **Kallonen J**, Corbascio M, Rådegran G, Bredin F, Sartipy U. Quality of life and functional status after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a Swedish single-center study. *Pulm Circ (In Press)*

Contents

1 Literature review 3
1.1 Incidence and prevalence of CTEPH 3
1.2 Risk factors for CTEPH 3
1.3 Pathophysiology 4
1.4 Symptoms 5
1.5 Diagnostics for CTEPH 5
1.5.1 Echocardiography 6
1.5.2 Ventilation/perfusion scintigraphy 7
1.5.3 Right heart catheterization 7
1.5.4 Imaging 7
1.6 Treatment of CTEPH 9
1.6.1 Anticoagulation 9
1.6.2 Vena cava filter 9
1.6.3 Balloon pulmonary angioplasty 9
1.6.4 Medical therapy 10
1.6.5 Surgery for CTEPH 11
1.7 Quality of life and functional status after PEA 14
1.7.1 Quality of life 14
1.7.2 Functional status 15
2 Research aims 17
3 Materials and methods 19
3.1 Study design 19
3.2 Study population 19
3.3 Data sources 19
3.3.1 Swedish Cardiac Surgery Registry and Swedeheart 20
3.3.2 SPAHR 20
3.3.3 Human Mortality Database 20
3.3.4 RAND-36 20
3.3.5 Karnofsky Performance Status 20
3.4 Statistical methods 21
3.4.1 Cumulative survival 21
3.4.2 Relative survival 22
3.4.3 Propensity scores 22
3.4.4 Inverse probability of treatment weighting 22
3.4.5 Flexible parametric survival models 22
3.4.6 Missing data 23
3.5 Ethical considerations 23

4 Results 25
4.1 Life expectancy after surgery for CTEPH 25
4.2 Sex and survival following PEA for CTEPH 29
4.2.1 Overall survival 29
4.2.2 Relative survival 32
4.3 Association of residual pulmonary hypertension with survival after PEA for CTEPH 33
4.3.1 Early mortality 35
4.3.2 Long-term survival 35
4.4 Quality of life and functional status after PEA 37
5 Discussion 43
5.1 Life expectancy after surgery for CTEPH 43
5.1.1 Limitations 44
5.2 Sex and survival following PEA for CTEPH 45
5.2.1 Limitations 47
5.3 Association of residual pulmonary hypertension with survival after PEA for CTEPH 48
5.3.1 Residual pulmonary hypertension and early mortality after PEA 48
5.3.2 Residual pulmonary hypertension—not related to long-term outcome? 48
5.3.3 Residual pulmonary hypertension—a prognostic marker for worse survival 49
5.3.4 Summary of residual pulmonary hypertension 50
5.3.5 Limitations 50
5.4 Quality of life and functional status after PEA 51
5.4.1 Quality of life after PEA 51
5.4.2 Functional status after PEA 54
5.4.3 Limitations 55
6 Conclusions 57
7 Future perspectives 59
8 Acknowledgements 61
9 References 63

List of abbreviations

BPA	balloon pulmonary angioplasty
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CI	confidence interval
CTEPH	chronic thromboembolic pulmonary hypertension
HR	hazard ratio
KPS	Karnofsky performance status
MCID	minimal clinically important difference
mPAP	mean pulmonary artery pressure
PAWP	pulmonary artery wedge pressure
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
QoL	quality of life
RHC	right heart catheterization
VTE	venous thromboembolism
V/Q scan	ventilation/perfusion scintigraphy
WHO FC	World Health Organization functional class
6MWT/D	six-minute walk test/distance

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease affecting a small portion of patients who survive acute pulmonary embolism. These patients often have vague symptoms, such as dyspnoea and fatigue, which makes it difficult to diagnose CTEPH.[1] Unresolved pulmonary emboli, intimal hypertrophy in the pulmonary arteries, and fibrotic transformation of clots leads to higher mean pulmonary artery pressure and increased pulmonary vascular resistance. Patients develop right heart failure, and untreated CTEPH can be lethal. In Swedish CTEPH patients the 5-year survival without surgical treatment is below 60% and the 8-year survival is approximately 40%.[2]

Most patients with CTEPH have a medical history of venous thromboembolism (i.e., deep vein thrombosis or pulmonary embolism). However, some patients debut with CTEPH without any history of previous venous thromboembolism. Known risk factors for CTEPH are repeated and unprovoked pulmonary embolism, young age, chronic inflammation, previous splenectomy, and infections in central venous catheters or pacemaker leads.[3,4]

The clinical picture of CTEPH has been recognized for almost 100 years. The first description of CTEPH was by Ljungdahl in 1928,[5] and in 1956 the disease was described by Hollister and Cull.[6] However, even today, CTEPH lacks a specific code in the International Classification of Disease.

According to the European Society of Cardiology guidelines for pulmonary hypertension, CTEPH is defined as at least one subsegmental perfusion defect on a ventilation/perfusion scintigraphy, typical findings on imaging, mean pulmonary artery pressure >20 mmHg at rest, pulmonary artery wedge pressure ≤15 mmHg, and pulmonary vascular resistance >2 Wood units.[1]

Pulmonary endarterectomy (PEA) is a potentially curative treatment for CTEPH, and inoperable patients may be treated by balloon pulmonary angioplasty or with medical therapy for symptomatic relief.

In this thesis, we compared long-term survival after PEA for CTEPH with that in a general population, assessed sex-specific survival after PEA, and investigated whether residual pulmonary hypertension in the early postoperative period is associated with long-term survival. We also evaluated quality of life and functional status late after PEA.

1 Literature review

1.1 Incidence and prevalence of CTEPH

Pulmonary embolism is considered to be the major risk factor for CTEPH. Keeping this in mind, it is important to note that up to 25% of patients who are diagnosed with CTEPH have no previous medical history of venous thromboembolism (VTE), including pulmonary embolism.[7]

It is difficult to examine the true incidence of pulmonary embolism in a population because of the heterogeneity of symptoms, which range from minor chest pain or cough to sudden cardiac death. Based on data from cohorts in Denmark, Sweden, and Canada, the incidence of pulmonary embolism is thought to range between 45 and 83 per 100,000 person-years.[8-10] Moreover, in the Danish cohort, the incidence of acute pulmonary embolism increased from 45 to 83 per 100,000 adult residents between 2004 and 2014.[8]

In prospective European cohort studies reported by Klok et al., Becattini et al., and Pengo et al., the cumulative incidence of CTEPH after acute pulmonary embolism was between 0.5% and 3.8%.[4,11,12] A review by Ende-Verhaar et al. in 2017 showed the incidence of CTEPH after acute pulmonary embolism to be in the range of 0.56%–3.2%.[13] A recent Chinese study published in 2018 found a much higher incidence of CTEPH after pulmonary embolism. In that study, the incidence of CTEPH was higher for subacute and chronic pulmonary embolism with a cumulative incidence of 14.5 % over 3 years.[14] According to The Swedish Pulmonary Arterial Hypertension Registry, the incidence of CTEPH in Sweden is 2–3 patients per million people annually.[15] A large European prospective multicentre study included 1098 patients with acute symptomatic pulmonary embolism and showed that the 2-year cumulative incidence of CTEPH after acute pulmonary embolism was 2.3%.[16]

Data on sex-related differences in the incidence of CTEPH are scarce. In the cohort of patients with acute pulmonary embolism investigated by Pengo et al., 58% were women and there was no sex-related difference in the incidence of CTEPH.[4] In the cohort investigated by Klok et al., 53% of 866 patients with acute pulmonary embolism were women. Only four patients developed CTEPH, three of whom were women.[11]

1.2 Risk factors for CTEPH

There are multiple known risk factors for developing CTEPH, which can be divided into two main categories, namely, factors causing acute pulmonary embolism and factors differing between patients with CTEPH and idiopathic pulmonary arterial hypertension.[17]

Major risk factors for CTEPH include repeated and unprovoked pulmonary embolism[13,18] as well as young or very old age at the time of detection of pulmonary embolism.[19] Patients with initial large perfusion defects on ventilation/perfusion (V/Q) scintigraphy are at increased risk of CTEPH, and right ventricular dysfunction at the time of acute pulmonary embolism is associated with the risk of developing CTEPH.[17,20] These phenomena probably reflect the difficulty of distinguishing between incident and prevalent CTEPH.

Medical conditions that are more common in the population with CTEPH than in the population with idiopathic pulmonary hypertension are often associated with chronic inflammation. Inflammation increases the risk of VTE and therefore the risk of CTEPH. The risk of CTEPH is increased in patients with an infection in a pacemaker lead or other central line and in those with a ventriculoatrial shunt.[18,19] Previous malignancy and splenectomy (all cause) are risk factors for developing CTEPH; the reason is believed to be induction of a hypercoagulable state because of inflammation. Blood group other than type O increases the risk of VTE and the likelihood of developing CTEPH.[18,21] Inflammatory bowel disease and osteomyelitis have been associated with an increased risk of CTEPH in some cohorts but not in all.[18] Association of thyroid replacement therapy and hypothyroidism with an increased risk of developing CTEPH have been confirmed by multiple cohort studies but the reason is unclear.[18,22] Many types of thrombophilia are overrepresented in VTE but only lupus anticoagulants or antiphospholipid antibodies are associated with actual development of CTEPH.[18,19]

1.3 Pathophysiology

The pathophysiology of CTEPH is as of yet not fully understood. Recurrent pulmonary embolism and incomplete resorption of pulmonary emboli leads to intimal hypertrophy in the pulmonary arteries and fibrotic transformation of clots, which lead to occlusions and stenoses in the vessels. This phenomenon is even thought to trigger so-called secondary small-vessel disease in the pulmonary arteries, which results in further increase in pulmonary vascular resistance, pulmonary hypertension, and finally right heart failure.[17] The mechanism of unresolved emboli is not clear. However, it has been speculated that a defect in fibrinolysis, thrombolysis, or angiogenesis may play a role.[23]

Dormüller et al. compared the histology of explanted lung tissue from 17 patients with CTEPH who had undergone lung transplantation for distal inoperable CTEPH or ineffective PEA with that in an experimental porcine model of CTEPH.[24] They found several types of vascular remodelling in the CTEPH lung that were not identified in the normal porcine lung. According to the author, the selection of patients in this study probably describes predominately microvascular disease. Extensive eccentric intimal fibrosis was seen in the

pulmonary arteries and organized thrombotic lesions were frequent. Interstitial remodelling with capillary haemangiomatosis-like foci was observed, and the pulmonary veins were also affected by intimal fibrosis. Intrapulmonary systemic vessels, the bronchial arteries, and the vasa vasorum were enlarged and hypertrophic. The bronchial arteries were connected to postcapillary pulmonary vessels causing bronchopulmonary venous shunting, which probably is an important mechanism in the pathophysiology of CTEPH.[24] These mechanisms could help to explain why PEA is unsuccessful in patients with distal lesions and high pulmonary vascular resistance in the absence of visible occlusions in the pulmonary arteries.

1.4 Symptoms

The symptoms of early CTEPH may be very vague. Patients often present with dyspnoea and fatigue but may also have haemoptysis, syncope, and signs of right heart failure.[1,25]

Symptoms of right heart failure include peripheral oedema, distension of the jugular vein, hepatojugular reflux, and hepatosplenomegaly, and may also include low cardiac output syndrome with hypotension, tachycardia, cool extremities, oliguria, and altered mentation.[26,27]

1.5 Diagnostics for CTEPH

According to the 2022 European Society of Cardiology (ESC) guidelines for pulmonary hypertension, the diagnostic work-up should start with a medical history, noting signs and symptoms indicating possible CTEPH (Figure 1). Patients who are symptomatic post-pulmonary embolism and have a systolic pulmonary artery pressure >60 mmHg on an echocardiogram should be investigated for CTEPH. Patients with suspected CTEPH should be treated with anticoagulants for at least 3 months to differentiate between subacute pulmonary embolism and CTEPH.[1] V/Q scintigraphy is then performed. This is the most effective scan to rule out CTEPH. If a V/Q mismatch is present in at least one segment CTEPH is a possible diagnosis.

The diagnosis needs to be confirmed by right heart catheterization (RHC) and typical findings for CTEPH on imaging. The patient is usually referred to an expert centre for RHC and advanced imaging for assessment of operability.

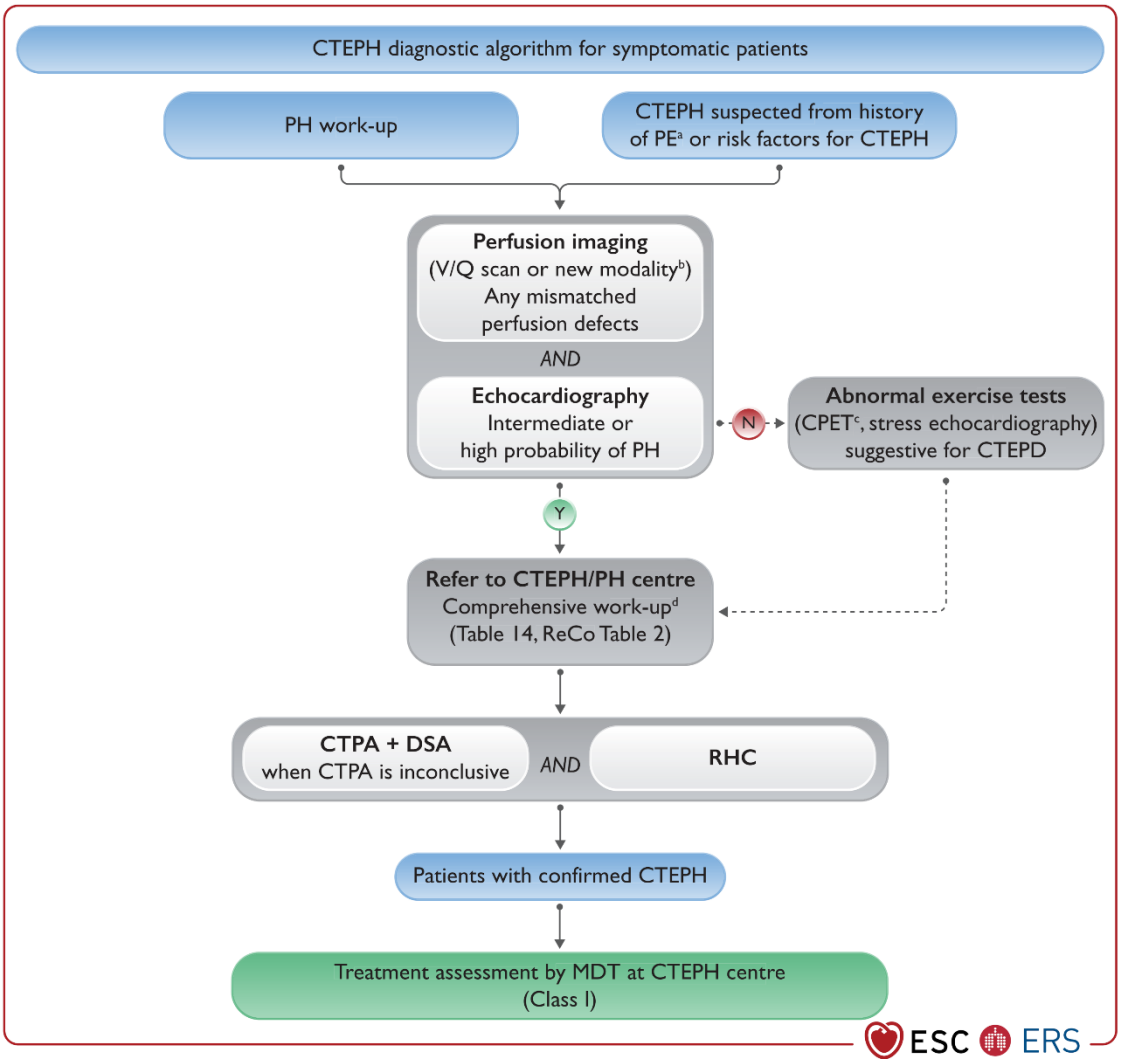


Figure 1. *Diagnostic strategy for CTEPH recommended by the European Society of Cardiology guidelines.[1] Reprinted with permission from Oxford University Press. CPET, cardiopulmonary exercise testing; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; DSA, digital subtraction angiography; MDT, multidisciplinary team; PE, pulmonary embolism; PH, pulmonary hypertension; V/Q, ventilation/perfusion.*

1.5.1 Echocardiography

Transthoracic echocardiography should be performed on patients with symptoms of possible CTEPH to find signs of pulmonary hypertension (estimated systolic pulmonary artery pressure) and right heart failure. A systolic pulmonary artery pressure of 60 mmHg on an echocardiogram indicates possible CTEPH.[1]

Pulmonary artery pressure is estimated by the trans-tricuspid pressure gradient. Right heart function is evaluated, and findings indicating right heart failure are dilatation, hypertrophy, hypokinesis, tricuspid regurgitation, right atrial enlargement, and septal deviation to the left during systole.[19,27,28]

1.5.2 Ventilation/perfusion scintigraphy

If CTEPH is suspected based on symptoms and elevated pulmonary artery pressure, a V/Q scan (also known as lung scintigraphy) is performed. The sensitivity of a V/Q scan for CTEPH is more than 96%.[29] If there are no areas or segments in the lung with mismatched ventilation and perfusion, CTEPH can be excluded as a differential diagnosis for pulmonary hypertension. The negative predictive value of a V/Q scan for CTEPH is nearly 100%.[29] If there is at least one subsegmental V/Q mismatch in the scan, CTEPH is a possible diagnosis and further examination is needed to confirm it. ESC guidelines for pulmonary hypertension recommend referring the patient to an expert pulmonary hypertension /CTEPH centre for further evaluation.[1,25]

1.5.3 Right heart catheterization

RHC is the gold standard for confirmation of pulmonary hypertension and for grading the severity of CTEPH.[30] The diagnostic criteria for CTEPH in RHC are mean pulmonary artery pressure (mPAP) of >20 mmHg at rest and a pulmonary artery wedge pressure (PAWP) of ≤15 mmHg, and pulmonary vascular resistance (PVR) >2 Wood units. PVR is also used to characterize the severity of the disease.[1,25] Heart function is measured by the cardiac index or cardiac output. RHC exercise testing can be used if CTEPH is suspected even if the mean pulmonary artery pressure at rest is below the threshold of 20 mmHg. In some patients, symptoms are caused by abnormal haemodynamic reactions, for example, a patient with a total unilateral occlusion of the pulmonary artery.[30,31] These patients, who have signs of fibrotic obstruction of the pulmonary arteries after VTE, but lacking pulmonary hypertension, are considered to have chronic thromboembolic pulmonary disease.[1]

1.5.4 Imaging

Diagnosis of CTEPH often requires use of multiple imaging modalities. Findings on imaging typical for CTEPH include ring-like stenoses, webs, slits, and occlusions in the pulmonary artery. Imaging can be performed using magnetic resonance imaging (MRI), computed tomography (CT), or conventional pulmonary angiography. Conventional pulmonary angiography is needed for assessment of operability. Imaging is essential to find alternative explanations for pulmonary hypertension, such as pulmonary artery sarcoma or parenchymal lung disease.

1.5.4.1 Pulmonary angiography

Pulmonary angiography is the gold standard imaging method for CTEPH and allows surgeons to visualize the anatomy of the pulmonary arteries in a practical straightforward way when assessing operability. Findings suggestive of CTEPH are webs, pouches, abrupt narrowings, obstructions and intimal irregularities in the pulmonary artery. If there are

central lesions, the patient is considered a surgical candidate for PEA. Only peripheral or distal lesions cannot be reached by surgery.[17,30]

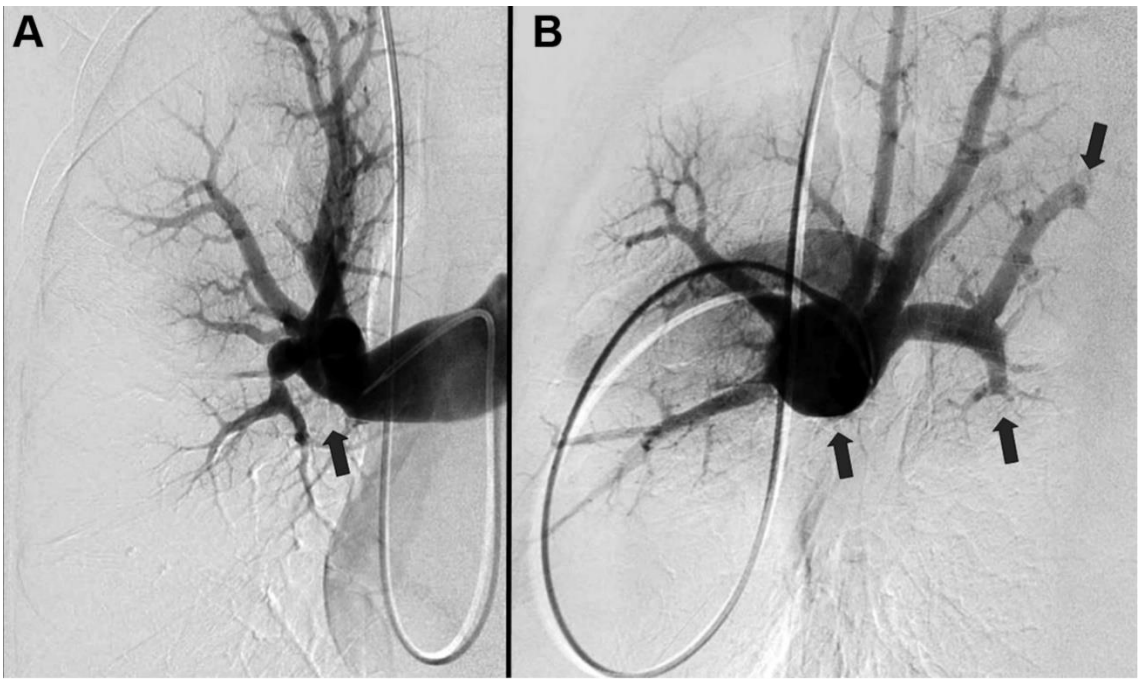


Figure 2. *Digital subtraction pulmonary angiography in chronic thromboembolic pulmonary hypertension. Arrows showing narrowings and occlusions in the pulmonary arteries.[17] Reprinted with permission from Elsevier.*

1.5.4.2 Magnetic resonance imaging

MRI is a versatile imaging modality that does not involve ionizing radiation, can assess heart function and lung perfusion, and allows visual imaging of the pulmonary artery tree, but is logistically more challenging than other methods used for imaging of CTEPH. Moreover, MRI is time-consuming, requires highly specialized radiologists for interpretation, and is difficult to access.[30]

1.5.4.3 Computed tomography

CT (or CT angiography) is the most easily accessible imaging modality. In experienced hands, CT has excellent accuracy for diagnosis of CTEPH. In comparison with conventional pulmonary angiography, Sugiura et al. found that CT could detect CTEPH with 97% sensitivity and specificity on a lobar level and with 86% sensitivity and 95% specificity on a segmental level.[32] In a Swedish study by Nordgren-Rogberg et. al., CT was reported to have a sensitivity of only 26% for diagnosis of CTEPH among general radiologists,[33] likely reflecting their poor knowledge of radiological findings for CTEPH. Findings indicating CTEPH include recanalized emboli in the pulmonary artery, organized thrombi, collateral blood flow

in arteries and a mosaic perfusion pattern.[17,32,34] CT is also important for differentiating CTEPH from other diseases in the chest.

1.6 Treatment of CTEPH

The ESC guidelines for pulmonary hypertension recommend that the diagnostic work-up for CTEPH be focused on both making the diagnosis of CTEPH and evaluating whether or not the patient is eligible for surgery.[1] Surgical treatment of CTEPH with PEA is the guideline recommended treatment. To date PEA is the only treatment for CTEPH improving patient prognosis. If the patient is inoperable, the patient is evaluated for symptomatic treatments such as medical treatment or balloon pulmonary angioplasty (BPA). Lifelong anticoagulation is required in all patients with CTEPH.[1] Treatment strategy is illustrated in Figure 3.

1.6.1 Anticoagulation

The first treatment for CTEPH is lifelong anticoagulation. Three months of anticoagulation is required to differentiate between subacute pulmonary embolism and CTEPH.[25] Warfarin has traditionally been used for anticoagulation, but novel oral anticoagulants (NOACs) are becoming increasingly popular because they are user-friendly and do not need monitoring of anticoagulation levels. However, there is limited evidence supporting the use of NOACs in CTEPH. Bunclark et al. retrospectively reviewed 1000 patients after PEA at the Royal Papworth Hospital in the United Kingdom (UK) and found that choice of anticoagulation did not affect functional and haemodynamic outcomes after PEA, and that bleeding complications and survival were similar in the groups.[35] However, significantly higher rates of VTE occurred in the patients treated with NOACs. Patients with antiphospholipid syndrome should be treated with warfarin.[36]

1.6.2 Vena cava filter

Vena cava filters were introduced in 1973 to prevent venous emboli from lower extremities to cause pulmonary embolism but there is limited evidence on efficacy and safety.[37] Many CTEPH centres no longer use these filters because no effect on long-term survival has been shown.[38]

1.6.3 Balloon pulmonary angioplasty

BPA is evolving as an alternative therapy for inoperable CTEPH. Technically inoperable patients with distal lesions and those with high surgical risk or recurrent pulmonary hypertension after PEA can be treated with BPA. Expert centres with broad experience of catheter-based therapies perform BPA in multiple procedures, usually 4–6 per patient, achieving good hemodynamic results while avoiding complications such as reperfusion oedema. BPA improves haemodynamics, exercise capacity, symptoms, and right ventricular

function.[17] In Japan, 30-day mortality was reported to be 2.6% after BPA.[39] Vascular injury, pulmonary artery perforation, haemothorax, and haemoptysis are common complications.[40]

1.6.4 Medical therapy

Drug therapy for CTEPH is limited. Riociguat, a soluble guanylate cyclase stimulator, is the only medical therapy approved for treatment of inoperable CTEPH. Riociguat acts on the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate (cGMP) signalling pathway resulting in vasodilatation.[41] In the CHEST-1 study, which included patients who were inoperable or had residual pulmonary hypertension after PEA, the 6-minute walk distance (6MWD) improved by 46 meters, PVR was decreased, markers of heart failure (such as B-type natriuretic peptide) were reduced, and patients improved in functional class.[42]

In the MERIT-1 and CTREPH trials, treatment with macitentan and high-dose trepostinil, respectively, showed some improvement in 6MWD and PVR. Macitentan is a dual endothelin receptor antagonist and trepostinil is a prostacyclin analogue. However, no long-term data to support an impact on survival were reported.[43,44]

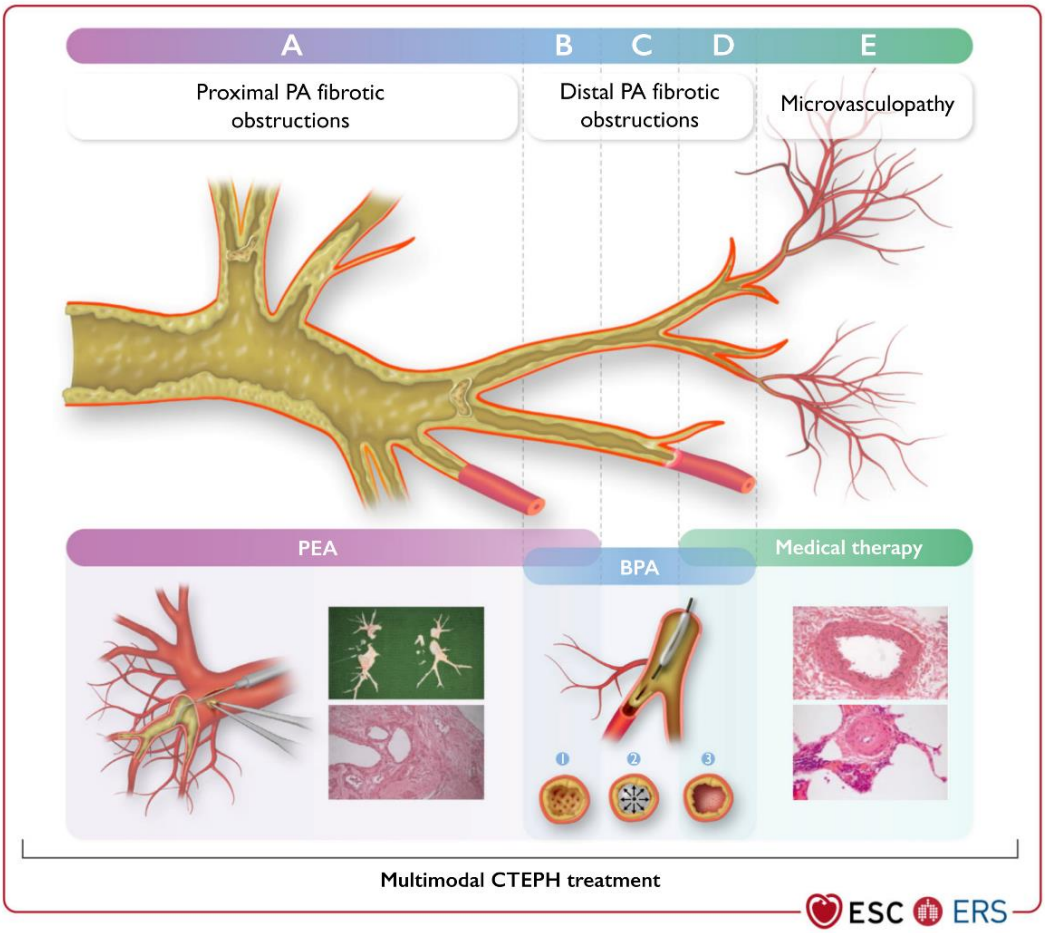


Figure 3. *Multimodal treatment of CTEPH.[1] Reprinted with permission from Oxford University Press. BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PA, pulmonary artery; PEA, pulmonary endarterectomy.*

1.6.5 Surgery for CTEPH

1.6.5.1 History

Cardiac surgery began to evolve during the 1950s with the development of the heart-lung machine, which made it possible to perform intracardiac procedures and more advanced cardiac surgery. The first successful open heart operation using a heart-lung machine was performed by Gibbon in 1953 in Philadelphia, for repair of an atrial septal defect in an 18-year-old woman.[45] Crafoord and Senning performed the second successful heart operation using cardiopulmonary bypass in Stockholm in 1954. The patient was a woman with atrial myxoma.[46,47] One of the first mechanical valves(ball and cage) was introduced in 1960 by Starr and Edwards,[48] and the first successful coronary artery bypass grafting surgery was by Favaloro at Cleveland Clinic in 1967.

The first successful PEA for CTEPH was performed in 1962 by Hufnagel,[49] who used a unilateral approach via a median sternotomy and with cardiopulmonary bypass on standby. The first PEA performed at University of California, San Diego (UCSD) was described by Moser et al., in 1973. The operation was performed by Dr Nina Braunwald in 1970 (the first female surgeon in the world to perform open heart surgery) and the surgical approach was via a lateral thoracotomy and used cardiopulmonary bypass.[50] Initially surgical access to the pulmonary artery was via lateral thoracotomy, and there was a widespread fear of reperfusion oedema, which subsequently led to only unilateral PEA being performed. During the 1970s and 1980s, the surgical technique at UCSD was refined by Daily, Uley, and Dembitsky, and the standard surgical approach by the 1990s was via median sternotomy using cardiopulmonary bypass and deep hypothermia with circulatory arrest.[51]

Early on, the only surgical option for CTEPH was double lung transplantation, which has the caveat of high morbidity and mortality because of immunosuppression, infection, and risk of rejection of the transplant. A paper by Jamieson et al. at UCSD in 2003 stated that lung transplantation was an outdated treatment option for CTEPH and reported excellent results from the PEA program at UCSD.[52]

1.6.5.2 Pulmonary endarterectomy

The surgical technique for PEA used today at the leading international centres (UCSD and Royal Papworth Hospital, Cambridge, UK) has been meticulously described by Madani et al. and Jenkins et al.[53,54] Their recommendation is that PEA should be performed bilaterally on the pulmonary arteries via median sternotomy and using cardiopulmonary bypass. Cannulation for cardiopulmonary bypass is in the distal ascending aorta and bicaval venous cannulation with vents for the left ventricle and the main pulmonary artery. Cooling is initiated when bypass is started. The patient is cooled to 18 degrees Celsius to facilitate circulatory arrest without brain damage.[55] Circulatory arrest is necessary to reduce blood flow

through the bronchial circulation, which would otherwise impede the surgeon's vision of the surgical field.

The right pulmonary artery is exposed between the aorta and the superior vena cava and a longitudinal incision is made. The correct layer for dissection (between lamina intima and media) is identified. This layer is usually described as pearly white and the easiest to dissect in. If the dissection is performed too deeply in the vessel wall, there is a risk of perforation of the pulmonary artery and fatal bleeding. Systematic endarterectomy with eversion technique is performed in all branches of the pulmonary arteries. The special instruments required for this operation are PEA forceps and a dissector with suction. After 20 minutes of circulatory arrest the body is reperfused, after which a new period of arrest can start. When the PEA on the right pulmonary artery is complete, the left pulmonary artery is incised, and endarterectomy is performed. Rewarming the patient to normal body temperature usually takes 90–120 minutes on cardiopulmonary bypass.[53]

The contraindications for PEA are relative. Severe chronic obstructive pulmonary disease and severe left heart failure are considered contraindications. However, there are risk factors for worse outcomes after PEA, including no history of VTE, World Health Organization functional class IV, right heart failure, PVR >15 Wood units, and absence of lower lobe disease.[56]

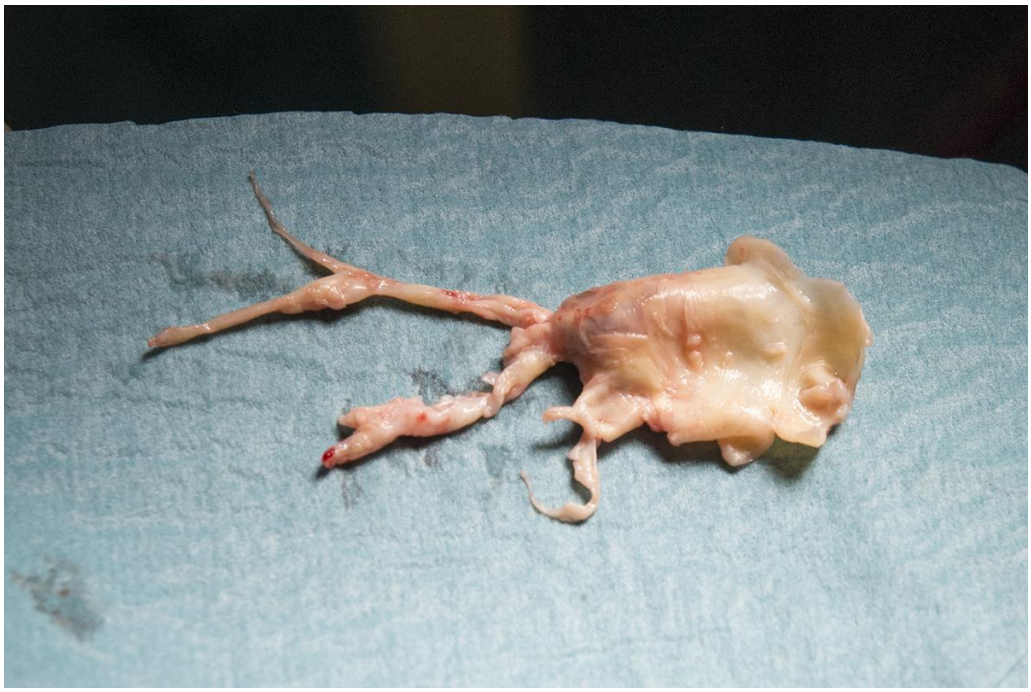


Figure 4. *Fibrotic tissue removed from a pulmonary artery. Photograph: Malin Jochumsen.*

1.6.5.3 Postoperative intensive care

Sophisticated cardiothoracic intensive care is required after PEA. Haemodynamics are monitored using a Swan-Ganz catheter and vasoactive drugs are used to provide inotropic support. Patients often develop hypoxaemia postoperatively because of redistribution of the circulation, resulting in V/Q mismatch and reperfusion oedema. Sometimes prolonged mechanical ventilation is needed, and non-invasive ventilation may be required after extubation.

Hypoxaemia can be treated with inhalation of nitric oxide, and circulatory mismatch may be improved by prostacyclin.[57] Reperfusion oedema occurs often within 72 hours of the operation. Aggressive diuresis is preferred for reduction of the risk of reperfusion oedema and is sometimes facilitated by dialysis or continuous renal replacement therapy. Extracorporeal membrane oxygenation (ECMO) is used when other treatment options for reperfusion oedema or right ventricular failure have failed.[17,58]

1.6.5.4 Surgical results

PEA is a potentially curative treatment for CTEPH. Many patients have improved haemodynamics postoperatively and report symptomatic relief. Functional testing also reveals improvement. Survival after PEA has improved dramatically. The 30-day mortality rate was reported to be 17% for the first 200 operations performed at UCSD [52] and 2,2% for the most recent 500 patients at UCSD in 2016.[53] High-volume expert centres are now operating on patients with more comorbidities and more distal lesions and with even lower mortality rates. In 2012, UCSD published data on 2700 patients who had undergone PEA. Survival data were obtained for 1410 of these patients, who had a 10-year survival of 75%.[59]

The Royal Papworth Hospital is the largest PEA centre in Europe. In a 2016 study by Cannon et al. that included 880 consecutive patients who underwent PEA between 1997 and 2012, the 1-year, 5-year, and 10-year survival rates were 86%, 79%, and 72% respectively.[60]

In an international prospective registry study reported by Delcroix et al., data were analysed for 679 patients treated at 27 centres in Europe and Canada between 2007 and 2009. PEA was performed in 404 of these patients. The 3-year survival rate was higher in patients who underwent PEA than in those who did not (89% vs 70%).[38]

Quadery et al. investigated operability and survival in 550 patients with recently diagnosed treatment-naive CTEPH and reported a 5-year survival rate of 83% after PEA. The group of patients who had technically operable CTEPH but were not offered surgery because of comorbidities or refused surgery had a 5-year survival of 53%. Patients with distal lesions that were considered technically inoperable had a 5-year survival rate of 59%.[61]

Sex-specific data after PEA are scarce. Barco et al. investigated sex-related differences in the 679 patients in the European CTEPH Registry, which included 339 women. Women underwent PEA less often than men but had better long-term survival (70/339 deaths [17%] vs 70/340 deaths [20,7%]).[62]

Cannon et al. and Madani et al. have reported improvement in patient haemodynamics and functional status after PEA.[59,60] In both cohorts, mean pulmonary artery pressure decreased from approximately 47 mmHg to 27 mmHg and 6MWD improved from 260 m to 353 m postoperatively.

1.7 Quality of life and functional status after PEA

It is difficult to ascertain the success of different therapies for CTEPH and to evaluate severity of disease. Therefore, it is incumbent on clinicians to develop various modalities to study clinical progression of the disease. Survival and haemodynamic measurements remain the corner stones for monitoring patients with CTEPH; however, patient-related outcome measures are also needed to obtain a broader picture of the disease and its treatment, and to evaluate the effects of treatment.

Given that a measurable difference in a patient-reported outcome is not always clinically relevant for the patient, the minimal clinically important difference (MCID) has been developed to describe the minimal change in a patient-reported outcome that is of value for the patient.[63]

1.7.1 Quality of life

1.7.1.1 Cambridge Pulmonary Hypertension Outcome Review

One tool developed specifically for measurement of quality of life (QoL) in patients with pulmonary hypertension is the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[64] This tool includes questions about QoL, symptoms, and limitations in activity, with maximum possible scores of 25, 25, and 30, respectively. These scores correlate negatively with the severity of symptoms or complaints (i.e., the lower the score, the better outcome).

CAMPHOR has been translated into Swedish and validated for use in Sweden.[65] CAMPHOR scores have been registered in the Swedish Pulmonary Arterial Hypertension Registry since 2010, and 68% of the patients included in the registry (pulmonary arterial hypertension and CTEPH) in 2019 completed the CAMPHOR. The MCID for the CAMPHOR score has been defined as -3 for activity, -4 for QoL, and -6 for symptoms.[66]

1.7.1.2 RAND-36

RAND-36 is currently used in many Swedish quality registries and is a free version of the Short Form-36 (SF-36). The SF-36 is the tool most widely used internationally for measurement of patient-reported outcomes.[67,68] In RAND-36, patients answer 36 questions in eight different domains divided into physical and psychological categories. The eight domains are general health (GH), bodily pain (BP), vitality (VT), physical functioning (PF), role physical (RP), mental health (MH), role emotional (RE), and social functioning (SF). Reference data are available for many populations and can be used for norm-based comparisons. The MCID for RAND-36 is considered to range between 3 and 5 points.[69]

1.7.2 Functional status

1.7.2.1 World Health Organization functional classification

The World Health Organization functional classification (WHO-FC) for pulmonary hypertension is similar to that used by the New York Heart Association (NYHA) to classify left-sided heart failure. It was created in 1998 at the World Symposium on Primary Pulmonary Hypertension and reported in the Executive Summary edited by Stuart Rich. The WHO functional classes for pulmonary hypertension were defined as follows:

WHO-FC I "Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope."

WHO-FC II "Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope."

WHO-FC III "Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope"

WHO-FC IV "Patients with PH with an inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity."[1,70]

There is wide variation in how clinicians assess WHO FC,[71] which may lead to difficulties when comparing patients with CTEPH and may also affect the choice of treatment.

1.7.2.2 Six-minute walk test

The 6MWT was developed in 1963 to assess functional capacity.[72] A useful and simple test that gives quantifiable values and can be repeated over time, the 6MWT is mostly used in patients with pulmonary disease or heart failure to investigate submaximal exercise capacity and is widely used during routine follow-up of both heart and lung failure. The 6-minute walk

distance (6MWD) has been reported to be 400–800 m in healthy adults, but the mean walking distance is usually 580–620 m.[73-75]

In the 6MWT the patient walks at a self-paced speed for 6 minutes on a hard flat surface that is at least a 30 m long, preferably indoors and where there is low traffic.[76] This simple test allows the clinician to study a patient's functional capacity in terms of disease progression and the success of therapy.

The MCID for the 6MWD in patients with pulmonary arterial hypertension was determined to be 33 m.[77] In a review that included patients with cardiac and pulmonary disease, the MCID was determined to be in the range of 14.0–30.5 m.[78]

1.7.2.3 Karnofsky Performance Status

The Karnofsky Performance Status (KPS) scale was originally developed in the 1940s to evaluate QoL in patients receiving chemotherapy[79] and is now used across multiple specialties. Using this tool, the patient's status is described in relation to their ability to perform normal activities and work on a scale from 0% to 100%. A score of 0% indicates the patient is deceased, a score of 50% indicates that the patient is unable to work but able to live at home and care for most personal needs but requires considerable assistance and frequent medical care, and a score of 100% describes a patients who is able to lead a normal day-to-day life with no signs of the illness.[80]

The KPS score has been related to NYHA, and especially in more severe disease stages the KPS seems to discriminate more accurately the patient's status.[81] Nevertheless, the KPS scale is not widely used in cardiovascular research.

2 Research aims

The overall aim of this thesis was to investigate long-term survival, quality of life, and functional status after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension.

The specific aims of the individual studies were:

Study I To compare long-term survival in patients undergoing PEA for CTEPH with that in the general population.

Study II To determine sex-specific survival after PEA in Scandinavia.

Study III To determine whether residual pulmonary hypertension, defined as an early postoperative mean pulmonary artery pressure ≥30 mmHg, after PEA for CTEPH was associated with worse long-term survival.

Study IV To assess and describe QoL and functional status after PEA for CTEPH.

3 Materials and methods

3.1 Study design

Studies I–III were observational cohort studies and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[82]

Study IV combined data from the Karolinska PEA cohort and information from a cross-sectional investigation of QoL and functional status of survivors post-PEA.

3.2 Study population

Study I included all patients who underwent PEA for CTEPH at Karolinska University Hospital between 1997 and 2018.

Studies II and III included all patients who underwent PEA for CTEPH at Karolinska University Hospital between 1992 and 2020 or at Aarhus University Hospital between 1994 and 2020.

Study IV included all patients who underwent PEA for CTEPH at Karolinska University Hospital between 1992 and 2020 and survived for longer than 30 days after the operation.

3.3 Data sources

All patients who underwent PEA at Karolinska University Hospital, Stockholm, Sweden, were enrolled in the studies. For the Swedish cohort, information on baseline characteristics and vital status was obtained from patient charts and completed with data from national health data registries, including the Swedish Pulmonary Arterial Hypertension Registry (SPAHR) and the Swedish Cardiac Surgery Registry,[83] using Swedish personal identity numbers.[84]

In *Studies II* and *III* the study populations comprised all patients who underwent PEA for CTEPH at either of two centres in Scandinavia (Karolinska University Hospital and Aarhus University Hospital, Aarhus, Denmark). The Danish study population was described in a previous study.[85] The baseline characteristics in the Danish cohort were obtained from patient charts and information on vital status was obtained for all patients through a search of the Danish Civil Registration System.[86]

3.3.1 Swedish Cardiac Surgery Registry and Swedeheart

All centres performing cardiac surgery in Sweden report to the Swedish Cardiac Surgery Registry. This registry received nationwide coverage in 1995 and was merged with Swedeheart[87] in 2009. The Swedish Cardiac Surgery Registry was recently validated and found to have good coverage and excellent reliability.[83]

3.3.2 SPAHR

The Swedish Pulmonary Arterial Hypertension Registry (SPAHR), is a national quality registry for pulmonary arterial hypertension and CTEPH.[15,88] This registry was launched in 2008, and all specialist centres for pulmonary arterial hypertension and CTEPH in Sweden report data into the SPAHR. Of 1782 incident and prevalent patients registered in the SPAHR, approximately 25% are patients with CTEPH. The 2020 SPAHR annual report identifies the completeness of data for RHC, 6MWT, WHO functional class, and CAMPHOR score at the time of diagnosis in patients with CTEPH for each referring centre in 2011 and 2016.[88] For example, in 2016, almost all patients with newly diagnosed CTEPH had undergone RHC and echocardiography, whereas CAMPHOR scores were only available for 15%–60% of patients who were registered.

3.3.3 Human Mortality Database

The Human Mortality Database (www.mortality.org) is an open access database, where researchers can find detailed information on population and mortality in 41 countries. Information on birth rates, population size, exposure to risk, death rates, and life tables is also available. Data from the Human Mortality Database were used in *Studies I* and *II* to estimate expected survival in the general population.

3.3.4 RAND-36

The RAND-36 questionnaire was used in *Study IV* and was sent by post to all patients who had undergone PEA at Karolinska University Hospital and were still alive. Patients who did not reply were sent a reminder and were contacted later by telephone if necessary.

3.3.5 Karnofsky Performance Status

All patients who answered the RAND-36 were contacted by telephone to conduct an interview for determination of the KPS score. The telephone interviews were conducted by a researcher or specialist nurse. The KPS is reported in S*tudy IV.*

Table 1. Overview of study design and methods.

	Study I	Study II		Study III		Study IV
Study design	Cohort	Cohort		Cohort		Cross-sectional, cohort
Cohort	Karolinska	Karolinska	Aarhus	Karolinska	Aarhus	Karolinska
Period	1997-2018	1992-2020	1994-2020	1992-2020	1994-2020	1992-2020
End of follow-up	April 1, 2019	May 6, 2021	Nov 16, 2020/ April 1, 2021	May 6, 2021	Nov 16, 2020/ April 1, 2021	March 2, 2022
Data sources	Patient charts, Swedeheart, Human mortality database	Patient charts, Swedeheart	Patient charts, Danish civil reg. system, Human mortality database	Patient charts, Swedeheart	Patient charts, Danish civil reg. system	Patient charts, Swedeheart, SPAHR, Self-reported quality of life, interview for KPS
Exclusion criteria	None	None		Missing early mPAP, dead within 30 days of PEA		Dead within 30 days of PEA
Number of patients	100	444		426		110
Exposure	PEA	Sex		Early postoperative mPAP ≥30 mmHg		
Outcome	All-cause mortality	All-cause mortality		All-cause mortality		Quality of life, functional status
Statistical method	Kaplan-Meier, Relative survival	Kaplan-Meier, Propensity score, Weighting, Flexible parametric survival models		Kaplan-Meier, Propensity score, Weighting, Flexible parametric survival models		Paired t-test

Aarhus, Aarhus University Hospital; KPS, Karnofsky Performance Status; mPAP, mean pulmonary artery pressure; PEA, pulmonary endarterectomy; SPAHR, Swedish Pulmonary Arterial Hypertension Registry.

3.4 Statistical methods

In all four studies in this thesis, the baseline characteristics are shown as the frequency and percentage for categorical variables and as the mean and standard deviations (SD) for continuous variables. In *Study IV*, measurements were compared using paired samples t-tests and reported as mean differences including 95% confidence intervals (CI). Data management and statistical analyses were performed using Stata versions 16.0 and 17.0 (StataCorp LP, College Station, TX, USA) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

3.4.1 Cumulative survival

The Kaplan-Meier method was used to calculate cumulative survival. In *Studies I, II,* and *III,* person time was calculated in days from the date of surgery until the date of death or end of follow-up. The end of follow-up for *Study I* was April 1, 2019. In *Studies II and III,* the end of follow-up was May 6, 2021 for the Swedish cohort, and either November 16, 2020 or April 1, 2021 for the Danish cohort.

3.4.2 Relative survival

Relative survival was used as an estimate for cause-specific mortality without the need for explicit information on cause of death. Relative survival was defined as observed survival of the study cohort divided by the expected survival.

The expected survival for the general population in Sweden in S*tudy I* was obtained from the Human Mortality Database and matched by age, sex, and year of surgery. In *Study II,* the expected survival for the general population in Denmark was also matched by age, sex, and year of surgery. The expected and observed survival curves were constructed with the strs Stata command using the Ederer II method.[89]

3.4.3 Propensity scores

Propensity scores are often used to compare treatments in nonrandomized groups. Propensity scores offer the possibility to adjust statistically for differences between groups and are defined as the probability (0–1) of treatment assignment based on the distribution of baseline characteristics.[90] There are four different methods for adjustment for baseline differences: matching, stratification, multivariable modelling, and weighting (or inverse probability of treatment weighting). Covariate balancing propensity scores were estimated to address confounding in *Studies II* and *III*.

3.4.4 Inverse probability of treatment weighting

In *Studies II* and *III, the* stabilized inverse probability of treatment weights were calculated to balance the differences in baseline characteristics in the two groups being compared.[91] The model included all the variables shown in Tables 3 and 5. Balance was assessed after weighting by standardized mean differences. An absolute standardized difference of ≤0.1 was considered an ideal balance.[92]

3.4.5 Flexible parametric survival models

Flexible parametric survival models are alternative models to the more traditional Cox proportional hazards model. They provide similar estimates, i.e., hazard ratios (HR), but with flexible parametric survival models other estimates, such as survival probabilities and survival differences, can be more easily obtained.[93]

In *Studies II* and *III,* flexible parametric survival models were used to estimate associations between the treatment group and reference group expressed as the HR and 95% CI before and after weighting. In the weighted populations, flexible parametric survival models were used to estimate survival and the absolute survival difference with a 95% CI between the groups.[94]

3.4.6 Missing data

There was no missing outcome data in *Studies I, II,* and *III.* In the weighted analyses, missing data were handled by constructing the weights so that the rates of missingness were balanced between the groups. In *Study III,* patients with missing exposure (measurement of early postoperative mPAP) were excluded from the analyses. In *Study IV,* patients with missing outcome data were excluded from the analyses.

3.5 Ethical considerations

All the studies in this thesis were approved by either the Regional Ethical Review Board in Stockholm or The Swedish Ethical Review Authority. The Central Denmark Region approved *Study II* and *III* according to the Danish Health Act paragraph 42, section 2. In *Study IV* informed consent was obtained from the patients for participation in RAND-36 and obtaining the KPS.

The main ethical consideration in the studies was patient privacy. Patient charts and medical records were reviewed to collect information for the study database. All health data are considered sensitive and treated accordingly. Limited access to the data and protection of the data is of the utmost importance.

Responsible interpretation of results is more important than ever before. Research and data are becoming more accessible to the members of the general public, who might lack the skills needed to interpret data. One of our responsibilities as researchers is to explain and interpret data and present results in a correct and ethical way.

4 Results

4.1 Life expectancy after surgery for CTEPH

Study I included 100 patients (61% male) with a mean age of 62 years (range 23–81) at time of surgery. Most patients were severely symptomatic before surgery, and 95% were in NYHA functional class III–IV. The mean body mass index was 26.6 (SD 5.0). Nineteen percent of the patients had preoperative concomitant chronic obstructive pulmonary disease, 5% of the patients had suffered a prior stroke, and kidney function was normal in 73%.

Before surgery, the mean systolic/diastolic pulmonary artery pressure was 78/27 mmHg and the mPAP was 45 mmHg (SD 11). None of the patients had severely depressed left ventricular ejection fraction, and 86% had normal left ventricular ejection fraction.

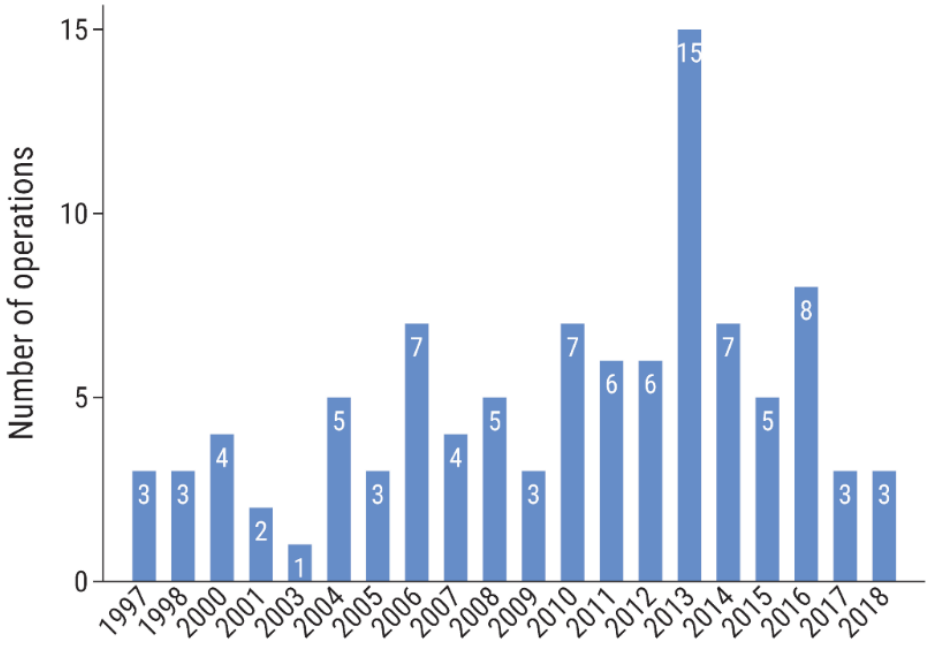


Figure 5. *Number of operations performed per year between 1997 and 2018 at Karolinska University Hospital.*

The mean and maximum follow-up times were 7.2 and 22.1 years, respectively. The 30-day mortality rate was 7%. At 5 years after PEA, the observed survival was 80% (95% CI 70–87), whereas the expected 5-year survival in the population matched for sex, age, and year of surgery was 92% (shown in Table 2). The relative survival at 5 years was 87% (95% CI 77–94). The observed, expected, and relative survival rates conditional on 30-day survival were, respectively, 86% (95% CI 77–92), 92%, and 94% (95% CI 83–100).

Table 2. Observed and expected mean 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	73 (57-87)
At 1 year	89	91 (83-95)	99	99 (93-100)
At 5 years	64	80 (70-87)	92	94 (83-100)
At 10 years	29	69 (57-78)	82	91 (75-100)
At 15 years	8	55 (40-68)	71	83 (60-100)
At 19 years	4	40 (20-59)	60	72 (36-100)
Sex				
Females	39	46 (28-63)	87	61 (37-81)
Males	61	58 (41-71)	76	82 (59-100)
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.

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

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

Kaplan-Meier estimated survival for the study population is shown in Figure 6, and Figure 7 illustrates observed survival and expected survival.

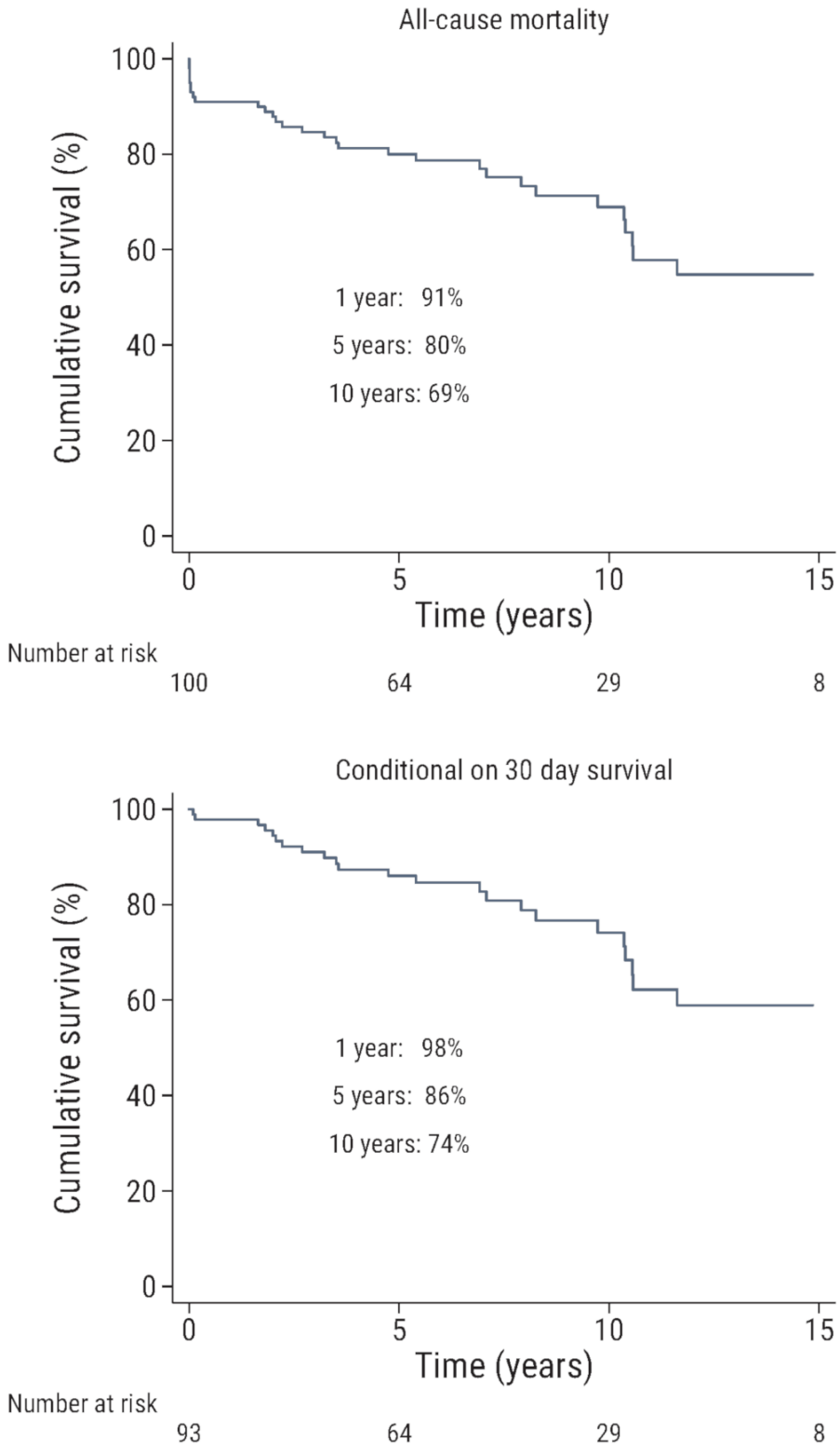


Figure 6. *Kaplan-Meier estimated survival in patients who underwent pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension between 1997 and 2018. The upper panel shows survival in the total study population, and the bottom panel shows survival conditional on patient survival beyond 30 days after pulmonary endarterectomy.*

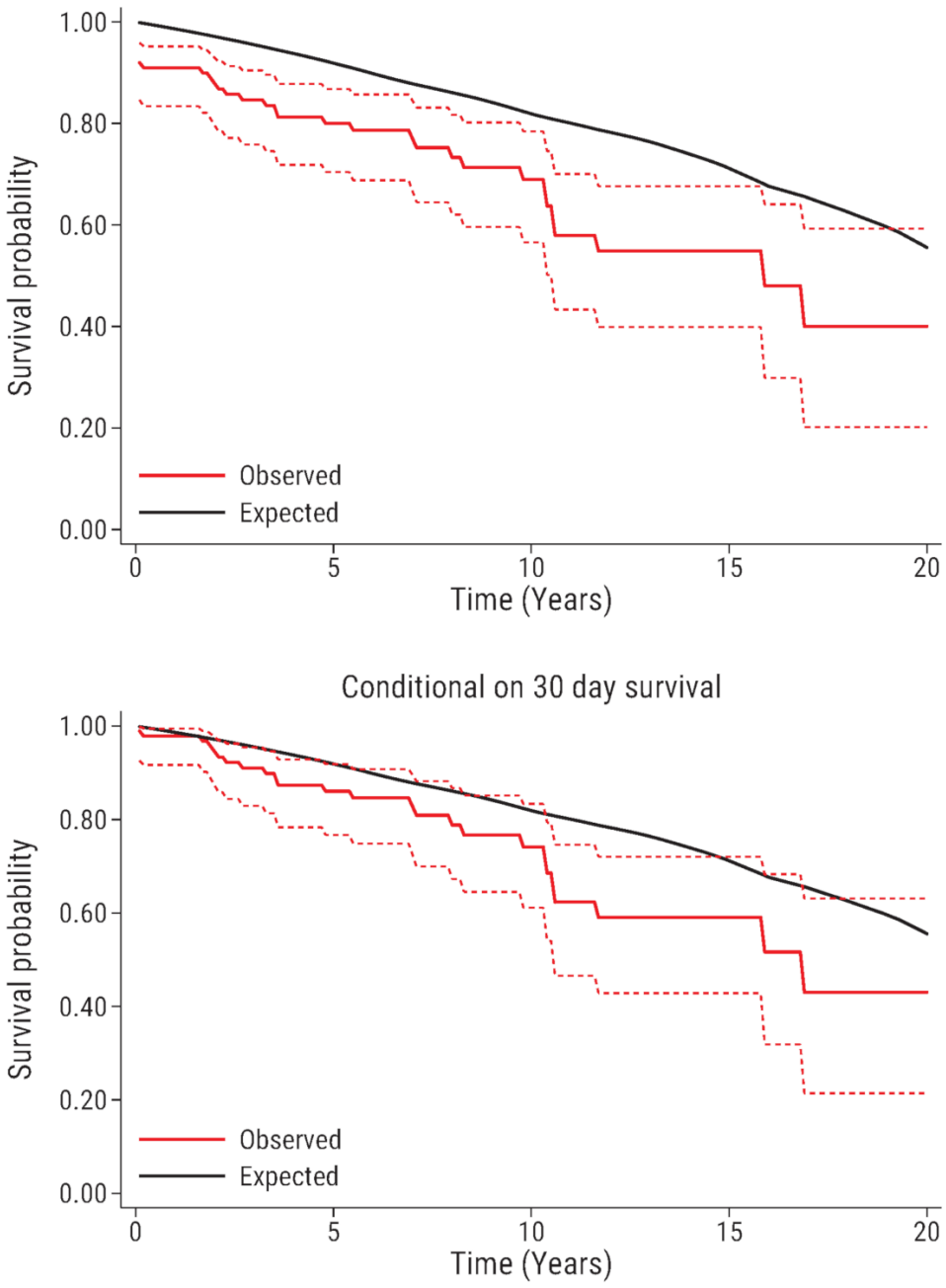


***Figure 7**. The observed survival (95% confidence interval) in patients after pulmonary endarterectomy (red solid line and red dashed lines) compared to the expected survival of an age-, sex-, and calendar-year matched Swedish population (black line). The upper panel shows the survival in the total study population (n=100), and the bottom panel shows the survival conditional on patient survival beyond 30 days after pulmonary endarterectomy (n=93).*

4.2 Sex and survival following PEA for CTEPH

A total of 444 patients were included in *Study II*. There were 184 women (41%) with a mean age of 59.2 years (SD 14.2) and 260 men (59%) with a mean age of 61.8 years (SD 12.2). The proportion of women undergoing PEA per year was relatively stable during the study period, with the exception of a couple of years. As shown in Table 3, there were differences in baseline characteristics between men and women before weighting. Women were younger and more likely to be active smokers and had more risk factors for VTE. Women were less likely to have coagulopathy or a history of VTE. Women were also more symptomatic at the time of surgery and were more likely to be on home oxygen therapy. Haemodynamic parameters were relatively similar in men and women.

4.2.1 Overall survival

The unadjusted all-cause 30-day mortality rate was 4.2% in men (11/260) and 9.8% in women (18/184) (p=0.020). Men and women were well-balanced for all baseline characteristics after inverse probability of treatment weighting; all standardized mean differences were <0.1. After weighting, the 30-day mortality rate was 4.6% in men and 12% in women (p=0.047).

The mean and maximum follow-up times in this study were 6.7 years (SD 6.2) and 25.9 years, respectively. The Kaplan-Meier estimated survival did not differ significantly between the sexes before weighting. Figure 8 shows the Kaplan-Meier estimated survival in the inverse probability of treatment-weighted population according to sex. The long-term survival did not differ significantly between the sexes after weighting (hazard ratio [HR] 1.36; 95% CI 0.89–2.06; p=0.153). Table 4 shows the 1-year, 5-year, 10-year, 15-year, and 20-year sex-specific survival (95% CI) in the weighted population and absolute survival differences. At all time points, the survival was better in men than in women; however, the difference was not statistically significant.

Table 4 also shows the sex-specific survival in the weighted population and the absolute survival difference (95% CI) after excluding the patients who died within 30 days of PEA. The differences between men and women who survived PEA and the early postoperative period were very small.

Table 3. Baseline characteristics in 444 patients who underwent pulmonary endarterectomy in Sweden and Denmark between 1992 and 2020.

Variable	Total population	Men	Women	p−value	Missing data (%)
Number of patients	444	260 (58.6)	184 (41.4)		0
Centre					
Denmark	324 (73.0)	185 (71.2)	139 (75.5)	0.359	0
Sweden	120 (27.0)	75 (28.8)	45 (24.5)		
Age (years), mean (SD)	60.7 (13.1)	61.8 (12.2)	59.2 (14.2)	0.039	0
Body mass index (kg/m^2)				0.362	29.1
<18.5	4 (1.3)	2 (1.0)	2 (1.7)		
18.5–24.99	119 (37.8)	74 (37.6)	45 (38.1)		
25–29.9	123 (39.0)	83 (42.1)	40 (33.9)		
≥30	69 (21.9)	38 (19.3)	31 (26.3)		
Smoking				0.003	0.2
Never	210 (47.4)	111 (42.9)	99 (53.8)		
Former	190 (42.9)	128 (49.4)	62 (33.7)		
Current	43 (9.7)	20 (7.7)	23 (12.5)		
COPD	31 (7.5)	15 (6.0)	16 (9.6)	0.249	6.5
Diabetes	12 (2.9)	9 (3.6)	3 (1.8)	0.427	6.5
Peripheral artery disease	7 (1.7)	4 (1.6)	3 (1.8)	1.000	6.5
Coagulopathy	61 (13.7)	44 (16.9)	17 (9.2)	0.029	0
Risk factor for VTE	38 (8.6)	15 (5.8)	23 (12.6)	0.019	0.7
History of VTE	354 (79.9)	219 (84.6)	135 (73.4)	0.006	0.2
WHO functional class				0.006	1.8
I–II	46 (10.6)	32 (12.5)	14 (7.8)		
III	316 (72.5)	192 (75.0)	124 (68.9)		
IV	74 (17.0)	32 (12.5)	42 (23.3)		
Poor mobility	6 (1.4)	3 (1.2)	3 (1.8)	0.943	6.5
6MWD (m), mean (SD)	356.8 (133.2)	379.7 (134.4)	326.3 (125.7)	0.001	33.3
Home oxygen therapy	61 (14.5)	27 (10.9)	34 (19.7)	0.018	5.4
PDEi treatment	76 (17.4)	36 (14.2)	40 (21.9)	0.052	1.8
Mean PAP (mmHg), mean (SD)	46.9 (10.8)	46.0 (10.3)	48.3 (11.2)	0.024	0.9
Cardiac index (l/min/m^2), mean (SD)	2.1 (0.5)	2.0 (0.5)	2.1 (0.6)	0.195	11.3
PAWP (mmHg), mean (SD)	10.3 (3.6)	10.3 (3.4)	10.2 (3.9)	0.678	16.0
PVR (dynes•s•cm^{-5}), mean (SD)	810.0 (404.2)	763.5 (406.4)	874.6 (393.2)	0.006	6.8
Endarterectomy reported as complete	370 (83.3)	221 (85.0)	149 (81.0)	0.322	0
Year of surgery				0.749	0
1992−2003	72 (16.2)	45 (17.3)	27 (14.7)		
2004−2011	164 (36.9)	94 (36.2)	70 (38.0)		
2012−2020	208 (46.8)	121 (46.5)	87 (47.3)		

Numbers are n (%) unless otherwise noted. 6MWD, six-minute walk distance; COPD, chronic obstructive pulmonary disease; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PDEi, phosphodiesterase inhibitors; PVR, pulmonary vascular resistance; SD, standard deviation; VTE, venous thromboembolism; WHO, World Health Organization.

Table 4. Survival in the total study population and according to sex with the absolute survival difference between men and women after pulmonary endarterectomy.

Time	Total population	Men	Women	Survival difference
Overall survival				
1 year	88 (83–93)	89 (85–94)	86 (80–92)	−3.6 (−8.6–1.5)
5 years	77 (72–82)	79 (73–86)	73 (66–81)	−6.3 (−15–2.4)
10 years	62 (56–69)	65 (58–74)	56 (47–67)	−9.2 (−22–3.5)
15 years	49 (42–57)	53 (44–64)	42 (33–55)	−11 (−25–3.9)
20 years	39 (31–50)	43 (32–57)	32 (21–47)	−11 (−26–4.0)
Conditional on 30–day survival				
1 year	96 (93–99)	96 (92–99)	95 (92–98)	−0.4 (−2.4–1.6)
5 years	85 (80–89)	85 (79–91)	83 (78–89)	−1.4 (−8.2–5.3)
10 years	67 (61–75)	68 (60–77)	65 (56–76)	−2.7 (−15–10)
15 years	53 (45–62)	54 (44–65)	51 (39–65)	−3.3 (−19–12)
20 years	43 (34–54)	43 (33–58)	40 (28–57)	−3.6 (−20–13)

Data are shown as % and (95% confidence interval) estimated from a flexible parametric survival model after inverse probability of treatment weighting.

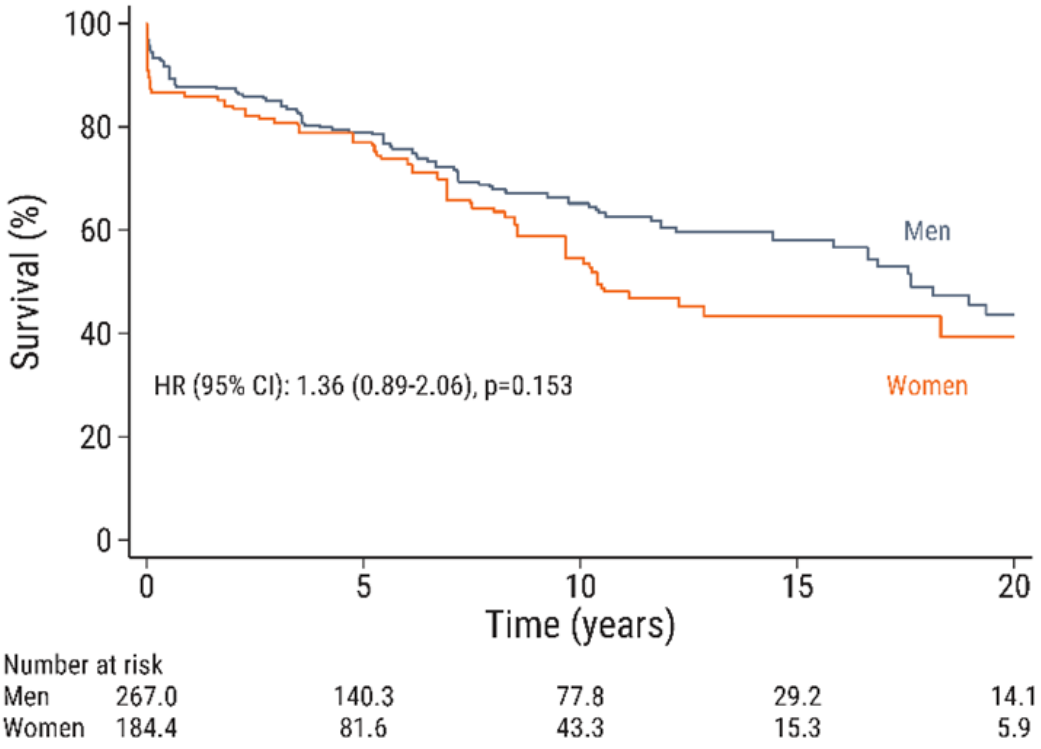


Figure 8. *Kaplan-Meier estimated survival in the inverse probability of treatment-weighted population according to sex. CI, confidence interval; HR, hazard ratio.*

4.2.2 Relative survival

During 15 years of follow-up relative survival in men ranged from 86% to 92%. The relative survival in women at 15 years after PEA was 67% (95% CI 53–80). Conditional on 30-day survival after PEA, relative survival ranged from 96% to 99% and was similar in men and women for up to 5 years of follow-up. In men, the relative survival at 5 and 10 years remained fairly stable at 90% and 94%, respectively. In women, the relative survival declined to 84% and 75%, respectively. The relative survival at 20 years was similar in men and women; however, owing to a small number of patients at this time point, any interpretations must be made with caution.

Figure 9 illustrates the observed and the expected survival for the total study population and that conditional on 30-day survival, according to sex. Both men and women had lower observed survival than expected survival. Observed survival in men was close to expected survival in the matched general population, however, in women, the difference was more pronounced. Women had a higher early mortality rate than men, and even if women who died within 30 days of PEA were excluded from analyses, there was a distinct difference between the observed survival rate and the expected survival rate after more than 5 years of follow-up.

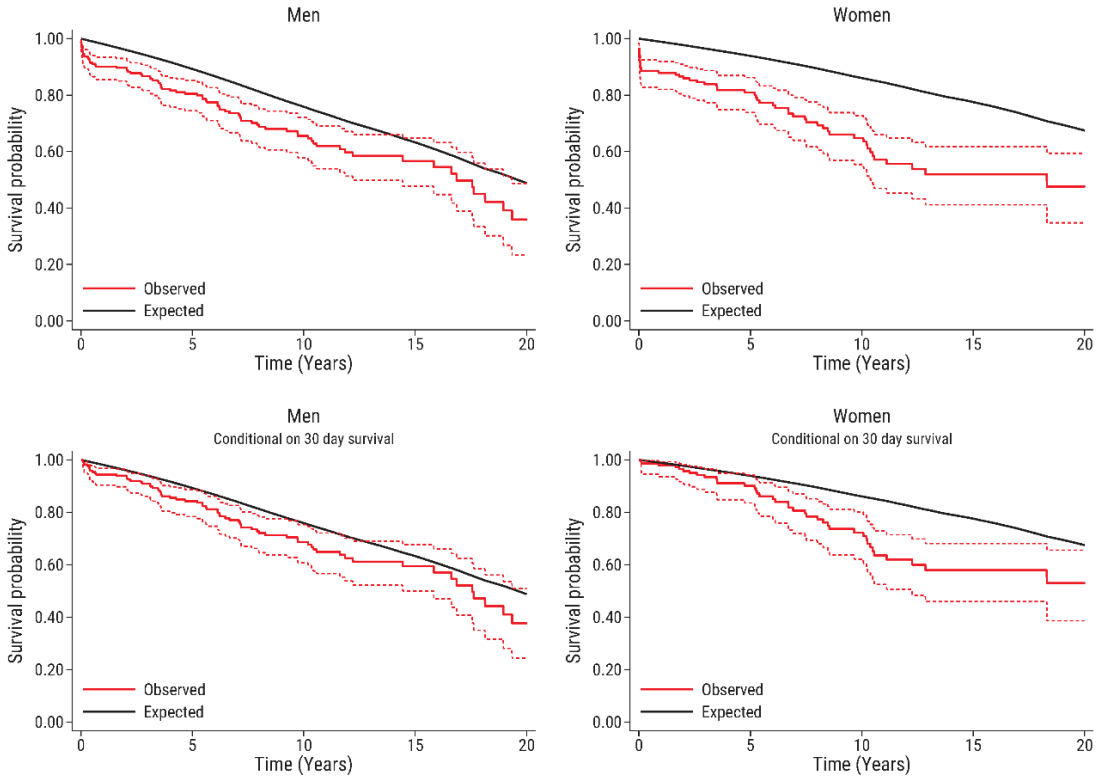


Figure 9. *Comparison of observed survival (95% confidence interval) in men and women after pulmonary endarterectomy (red solid line and red dashed lines) with expected survival in a Danish population matched for age, sex, and calendar year (black line). The upper panel shows survival in the total study population (n=444) and the bottom panel shows survival conditional on patient survival beyond 30 days after pulmonary endarterectomy (n=415).*

4.3 Association of residual pulmonary hypertension with survival after PEA for CTEPH

Study III included 444 patients who underwent PEA for CTEPH at either of two Scandinavian centres. The final study population comprised 426 patients after excluding six patients who died on the day of PEA, and 12 patients with no information regarding early postoperative mPAP (measurement within 48 h after undergoing PEA).

Baseline characteristics are shown in Table 5. The mean age for the patients at the time of surgery was 60.6 years (SD 13.2), and 41% of the study participants were women. The early postoperative mPAP was <30 mmHg in 174 patients (41%), and ≥30 mmHg in 252 patients (59%). The distribution of early postoperative mPAP values is shown in Figure 10. The annual proportion of patients who had early postoperative mPAP ≥30 mmHg decreased slightly during the study period.

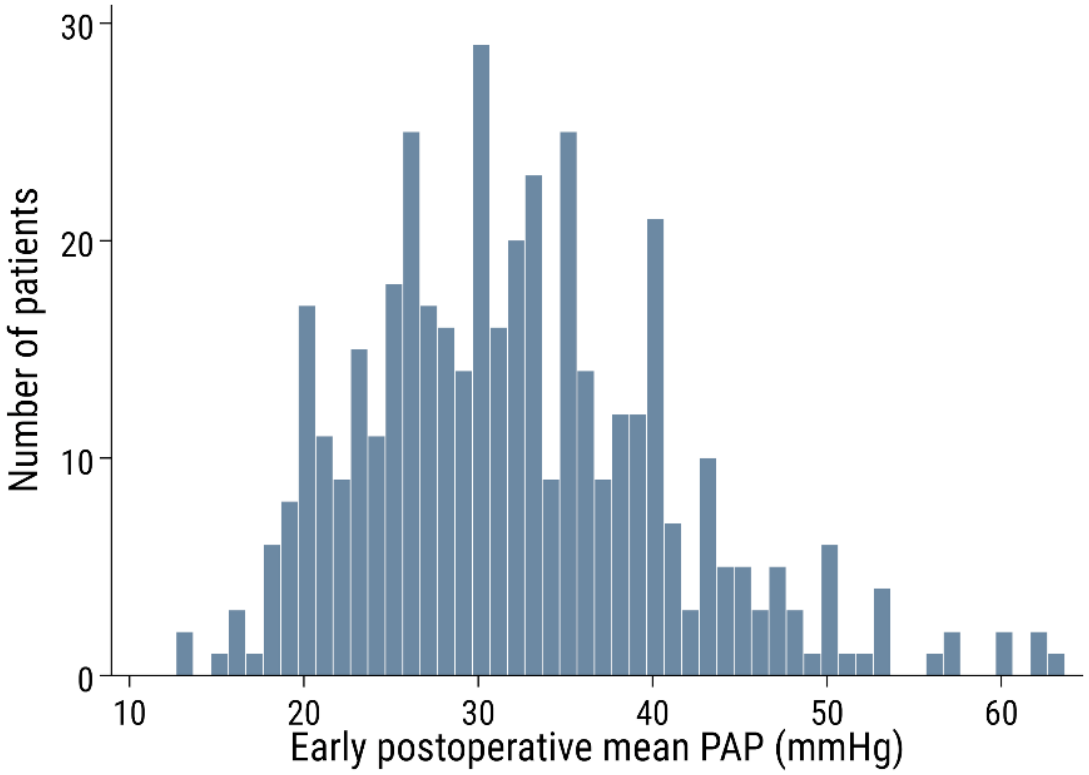


Figure 10. *Distribution of early postoperative mean PAP in the study population. PAP, pulmonary artery pressure.*

Table 5. Baseline characteristics in 426 patients who underwent pulmonary endarterectomy in Sweden and Denmark between 1993 and 2020.

Variable	Total population	Early postoperative mean PAP		p-value	Missing data (%)
		<30 mmHg	≥30 mmHg		
Number of patients	426	174	252		
Centre				0.804	0.0
Denmark	310 (72.8)	125 (71.8)	185 (73.4)		
Sweden	116 (27.2)	49 (28.2)	67 (26.6)		
Age (years), mean (SD)	60.6 (13.2)	60.0 (14.4)	61.0 (12.4)	0.462	0.0
Female sex	176 (41.3)	60 (34.5)	116 (46.0)	0.023	0.0
Body mass index (kg/m^2)				0.332	27.9
<18.5	4 (1.3)	1 (0.7)	3 (1.8)		
18.5–24.99	118 (38.4)	47 (34.6)	71 (41.5)		
25–29.99	117 (38.1)	59 (43.4)	58 (33.9)		
≥30	68 (22.1)	29 (21.3)	39 (22.8)		
Smoking				0.152	0.2
Never	200 (47.1)	87 (50.0)	113 (45.0)		
Former	183 (43.1)	66 (37.9)	117 (46.6)		
Current	42 (9.9)	21 (12.1)	21 (8.4)		
COPD	30 (7.5)	14 (8.6)	16 (6.8)	0.618	6.6
Diabetes	11 (2.8)	4 (2.5)	7 (3.0)	1.000	6.6
Peripheral artery disease	7 (1.8)	2 (1.2)	5 (2.1)	0.786	6.6
Coagulopathy	58 (13.6)	31 (17.8)	27 (10.7)	0.050	0.0
Risk factor for VTE	37 (8.7)	13 (7.5)	24 (9.6)	0.568	0.7
History of VTE	341 (80.2)	150 (86.2)	191 (76.1)	0.014	0.2
WHO functional class				<0.001	1.9
I–II	45 (10.8)	28 (16.3)	17 (6.9)		
III	303 (72.5)	130 (75.6)	173 (70.3)		
IV	70 (16.7)	14 (8.1)	56 (22.8)		
Poor mobility	6 (1.5)	4 (2.5)	2 (0.8)	0.376	6.6
6MWD (m), mean (SD)	357 (133)	394 (128)	330 (131)	<0.001	32.2
Home oxygen therapy	57 (14.2)	15 (9.0)	42 (17.9)	0.018	5.6
PDEi treatment	75 (17.9)	25 (14.7)	50 (20.1)	0.201	1.6
Mean PAP (mmHg), mean (SD)	47 (11)	43 (11)	50 (10)	<0.001	0.9
Cardiac index (l/min/m^2), mean (SD)	2.1 (0.5)	2.2 (0.6)	2.0 (0.5)	0.001	11.0
PCWP (mmHg), mean (SD)	10 (3.6)	9.8 (3.4)	11 (3.7)	0.039	15.7
PVR (dynes•s•cm^{-5}), mean (SD)	808 (403)	656 (291)	916 (437)	<0.001	6.6
Endarterectomy reported as complete	358 (84.0)	159 (91.4)	199 (79.0)	0.001	0.0
Year of surgery				0.006	0.0
1992−2003	63 (14.8)	16 (9.2)	47 (18.7)		
2004−2011	163 (38.3)	63 (36.2)	100 (39.7)		
2012−2020	200 (46.9)	95 (54.6)	105 (41.7)		

Numbers are n (%) unless otherwise noted. 6MWD, six-minute walk distance; COPD, chronic obstructive pulmonary disease; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PDEi, phosphodiesterase inhibitors; PVR, pulmonary vascular resistance; SD, standard deviation; VTE, venous thromboembolism; WHO, World Health Organization.

As shown in Table 5, the baseline characteristics differed between patients with early postoperative mPAP <30 mmHg and the patients with early postoperative mPAP ≥30 mmHg before weighting. Patients with an early postoperative mPAP ≥30 mmHg were more often women, were more symptomatic in terms of WHO functional class, had a shorter 6MWD, and were more frequently on home oxygen treatment, and were more likely to have been treated with phosphodiesterase inhibitors before PEA. They also had a higher preoperative PVR, higher mPAP and a lower cardiac index, as well as the endarterectomy procedure being reported as complete less often. All baseline characteristics were well balanced across the groups after weighting.

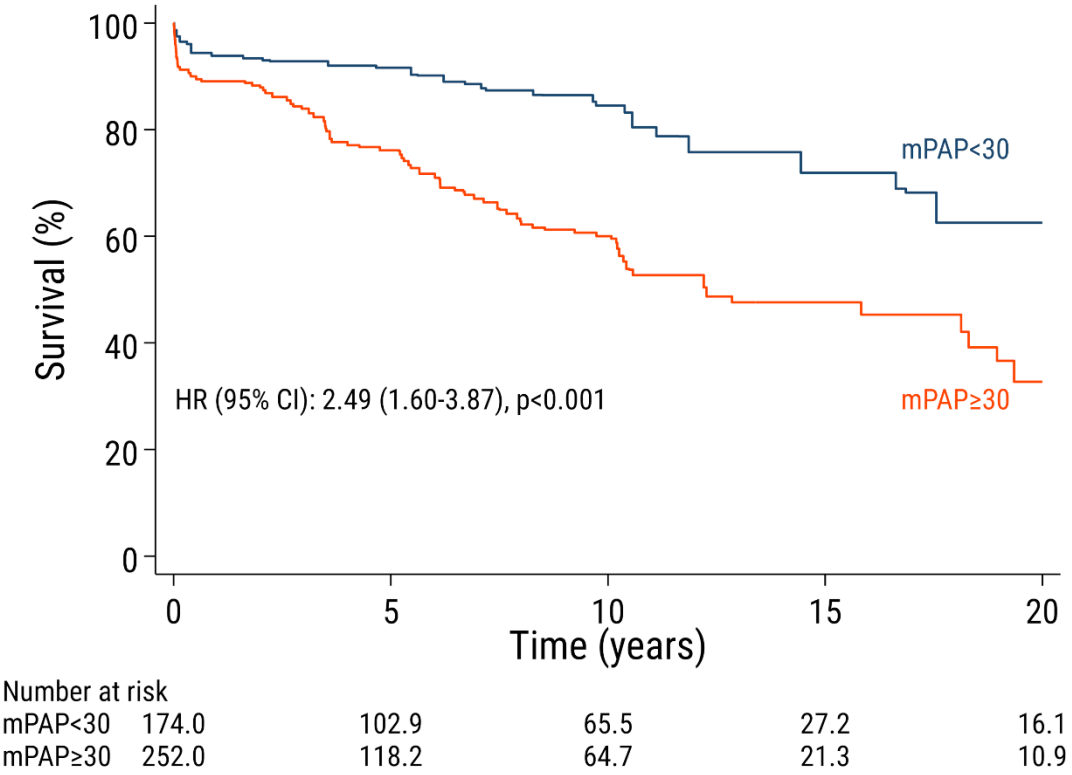
4.3.1 Early mortality

The unadjusted all-cause 30-day mortality rate was 1.7% (3/174) in patients with early postoperative mPAP <30 mmHg and 7.5% (19/252) in the patients with early postoperative mPAP ≥30 mmHg (p=0.008). The 30-day mortality rate after weighting was lower when early postoperative mPAP was <30 mmHg than when it was ≥30 mmHg (2.4% vs. 6.5%; p=0.095).

4.3.2 Long-term survival

The mean and maximum follow-up times for the study population were 6.8 years (SD 6.1) and 25.9 years, respectively. A significant difference in Kaplan-Meier estimated survival was seen before weighting between the groups (HR 2.09; 95% CI 1.42–3.07; p<0.001). Figure 11 shows the Kaplan-Meier estimated survival in the weighted population. There was a significant difference in long-term survival according to whether early postoperative mPAP was <30 mmHg or ≥30 mmHg (HR 2.49; 95% CI 1.60–3.87; p<0.001). In the weighted population, survival was significantly better at all time points in patients with early postoperative mPAP <30 mmHg than in those with early postoperative mPAP ≥30 mmHg. Survival was 81% (95% CI 74–88) in patients with early postoperative mPAP <30 mmHg and 59% (95% CI 52–68) in those with early postoperative mPAP ≥30 mmHg at 10 years of follow-up. At 10 years, the absolute survival difference was -22% (95% CI -32 to -12).

The long-term survival conditional on 30-day survival after PEA was significantly better when the early postoperative mPAP was <30 mmHg than when it was ≥30 mmHg at all time points up to 20 years.



Number at risk

mPAP<30	174.0	102.9	65.5	27.2	16.1
mPAP≥30	252.0	118.2	64.7	21.3	10.9

Figure 11*. Kaplan-Meier estimated survival according to postoperative mPAP after pulmonary endarterectomy in the weighted population. CI, confidence interval; HR, hazard ratio; mPAP, mean pulmonary artery pressure.*

4.4 Quality of life and functional status after PEA

Study IV included 110 patients who underwent PEA for CTEPH between 1992 and 2020 at Karolinska University Hospital and survived beyond 30 days after PEA. The RAND-36 questionnaire was sent by post to all 66 patients who remained alive in September 2020. Sixty-one patients were alive at the end of follow-up on March 2, 2022. The RAND-36 questionnaire was completed by 49 patients, 42 of whom provided a KPS score via telephone interview.

Table 6 shows the baseline characteristics for the study population. The mean age at the time of PEA was 61.2 years and 65% of the patients were men. At the time of surgery, 51% were never-smokers, 45% were former smokers, and 5% were active smokers. Twenty-two percent of the study population were preoperatively diagnosed with chronic obstructive pulmonary disease. Diabetes was diagnosed in 2.7% and 5.5% had peripheral artery disease. A history of VTE was present in a majority (92%) of patients, although only 7.3% had known risk factors. Twenty-two percent had been preoperatively diagnosed with coagulopathy. The mean 6-minute walk test was preoperatively 362 m, and 89% of patients were in WHO functional class III–IV. Home oxygen therapy was administered to 19% of the patients, and 15% had been on phosphodiesterase inhibitors before surgery. The mean preoperative mPAP was 46 mmHg, and the mean cardiac index was 2.1 l/min/m^2.

Preoperative and postoperative results for the 6MWT were available for 51 of 110 patients (64%). The mean time from preoperative 6MWT to late measurement was 5.5 years (range 0.2–19). The mean 6MWD was 378 m before surgery and 410 m late after PEA. The mean difference was 32 m (95% CI -4.7 to 69; p=0.086).

Evaluation of mPAP and cardiac index by RHC, both preoperatively and postoperatively, was available for 39 of 110 patients (35%) and 35 of 110 patients (32%), respectively. The mean time from preoperative RHC to late postoperative measurements was 6.0 years (range 0.9–17). The mean difference in mPAP was -13 mmHg (95% CI -16 to -10). The mean difference in cardiac index was 0.4 l/min/m^2 (95% CI 0.2–0.6).

Table 6. Baseline characteristics in 110 patients who underwent pulmonary endarterectomy in Sweden between 1993 and 2020.

Variable	Total population	Missing data (%)
n	110	
Age (years), mean (SD)	61.2 (12.6)	0.0
Female sex	39 (35.5)	0.0
Body mass index (kg/m^2)		0.0
<18.5	0	
18.5-24.99	48 (43.6)	
25-29.9	43 (39.1)	
≥30	19 (17.3)	
Smoking		0.0
Never	56 (50.9)	
Former	49 (44.5)	
Smoker	5 (4.5)	
COPD	24 (21.8)	0.0
Diabetes	3 (2.7)	0.0
Peripheral artery disease	6 (5.5)	0.0
Coagulopathy	24 (21.8)	0.0
Risk factor for VTE	8 (7.3)	0.0
History of VTE	101 (91.8)	0.0
WHO functional class		0.9
I–II	12 (11.0)	
III	80 (73.4)	
IV	17 (15.6)	
Poor mobility	4 (3.6)	0.0
6MWD (m), mean (SD)	362.4 (144.6)	61.8
Home oxygen therapy	21 (19.3)	0.9
PDEi treatment	16 (15.1)	3.6
Mean PAP (mmHg), mean (SD)	45.8 (9.8)	0.0
Cardiac index (l/min/m^2), mean (SD)	2.1 (0.5)	10.0
PCWP (mmHg), mean (SD)	10.0 (3.2)	24.5
PVR (dynes•s•cm^{-5}), mean (SD)	743.1 (302.6)	1.8
Endarterectomy reported as complete	94 (85.5)	0.0
Year of surgery		0.0
1993-2003	24 (21.8)	
2004-2011	39 (35.5)	
2012-2020	47 (42.7)	

Numbers are n (%) unless otherwise noted. 6MWD, six-minute walk distance; COPD, chronic obstructive pulmonary disease; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PDEi, phosphodiesterase inhibitors; PVR, pulmonary vascular resistance; SD, standard deviation; VTE, venous thromboembolism; WHO, World Health Organization.

The RAND-36 questionnaire was completed by 49 of 66 patients (74%). The mean time from PEA to evaluation of QoL by the RAND-36 was 8.5 years (range 1–24). The results from the study population and the Swedish age-matched population are shown in Figure 12. The patients who had undergone PEA had slightly lower scores than the reference population in all domains except for bodily pain. The domains that were most affected were physical functioning and role physical.

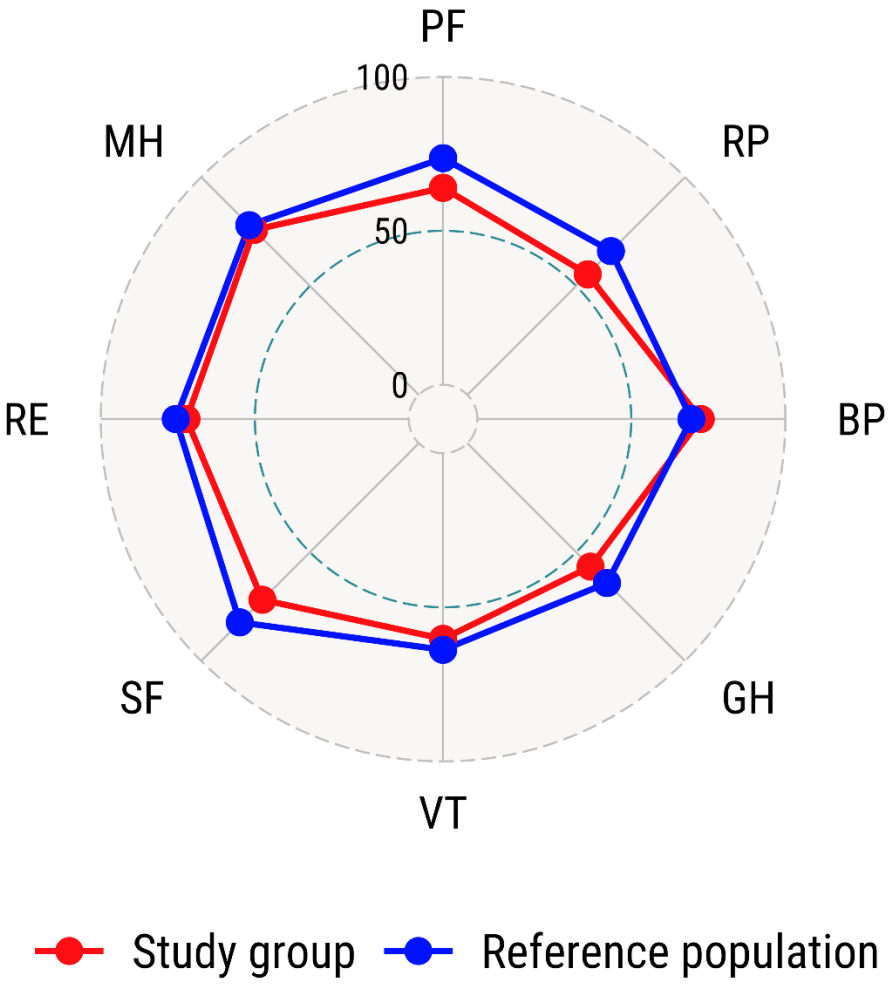


Figure 12. *Health-related quality of life according to RAND-36 scores in 49 patients at late follow-up after pulmonary endarterectomy (red line) and an age-matched Swedish reference population (blue line). BP, bodily pain; GH, general health; ME, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.*

The KPS score was obtained for 42 of 49 patients (86%). Twelve (29%) of these patients, had a KPS score of 100%, and 31 (74%) had a score of 80% or higher (i.e., "able to carry on normal activity"). The KPS scores for the study population are shown in Figure 13. All study participants were able to live at home and care for most of their personal needs, although 11of them (26%) were unable to carry on normal activities and work.

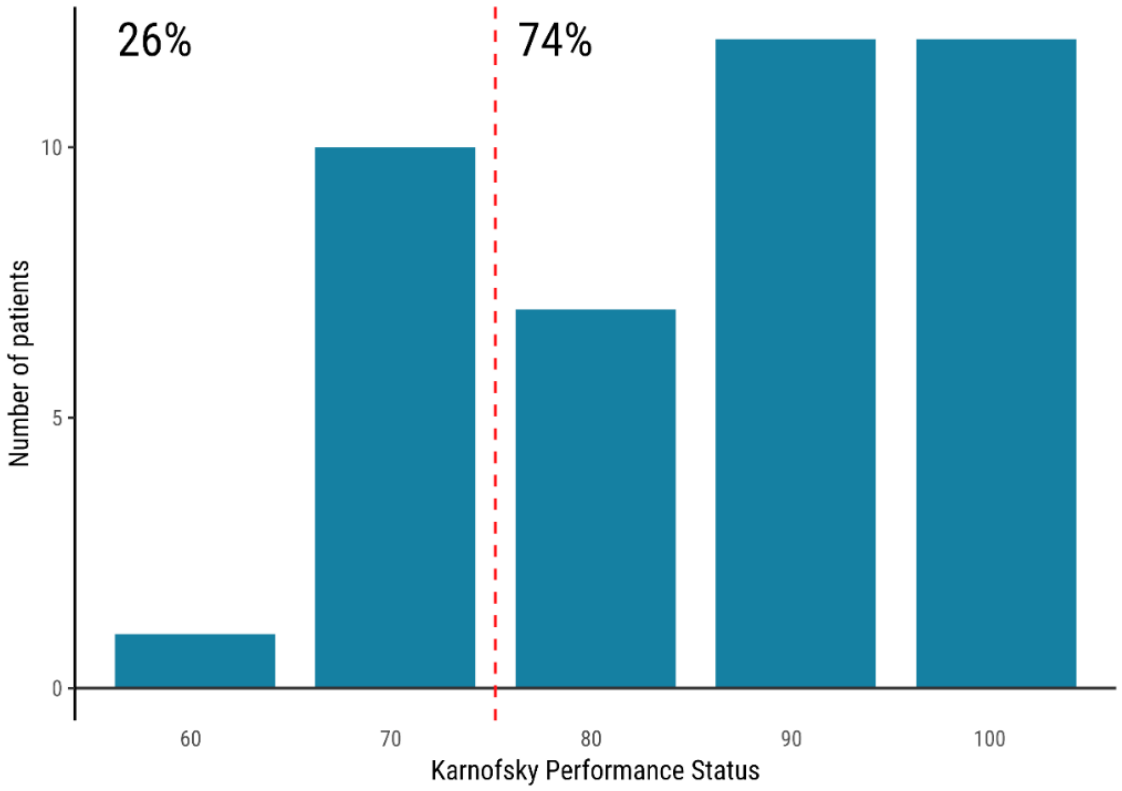


Figure 13. *Functional status according to the Karnofsky Performance Status (KPS) score in 42 patients at late follow-up after pulmonary endarterectomy. In 74% of the patients, the KPS score was ≥80% (i.e., "able to carry on normal activity").*

Postoperative data on CAMPHOR were available for 47 of 110 patients (43%). The results are shown in Figure 14. The mean time from surgery to evaluation by CAMPHOR was 5.9 years (range 0.4–20). The median CAMPHOR scores after PEA were 4 for symptoms, 4 for activity, and 2.5 for QoL.

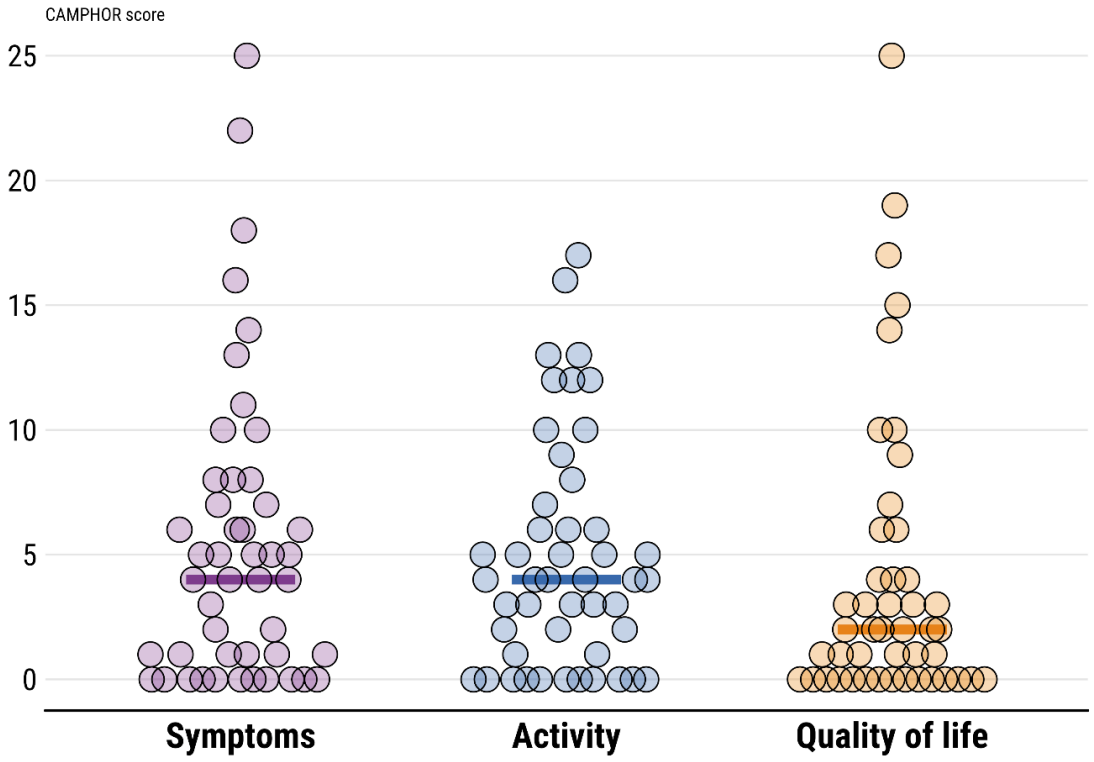


Figure 14. *The distribution of CAMPHOR scores in 47 patients after pulmonary endarterectomy across the three domains of symptoms, activity, and quality of life. Circles represent individual patients, and the thick lines represent the median CAMPHOR score. CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review.*

5 Discussion

This thesis investigated long-term survival as well as QoL and functional status after PEA for CTEPH. PEA improves life expectancy and patients enjoy a nearly normal QoL and functional status. Patients without early postoperative residual pulmonary hypertension have a better long-term prognosis, and there are no significant sex-related differences in prognosis post-PEA after adjustment for baseline characteristics.

5.1 Life expectancy after surgery for CTEPH

The prognosis for patients with untreated CTEPH is poor. The outlook for those on medical therapy or treated with BPA has improved, but patients with CTEPH that are not treated surgically by PEA have a 3-year survival rate of 70%,[38] a 5-year survival rate below 60%,[2] and a 10-year survival rate of 40%.[95] In high-volume PEA centres, in-hospital mortality has decreased after PEA from 17%[52] to just over 2% in recent cohorts.[59,60] Long-term (5-year) survival after PEA is approximately 80% and 10-year survival is approximately 70%-75%.[59,60] PEA has previously been called a "curative" treatment for CTEPH, but survival after PEA had not been compared with that in a general population before now. Therefore, we compared life expectancy between the post-PEA population and a Swedish general population matched for age and year of surgery.

In *Study I,* we found that life expectancy following PEA for CTEPH was shorter than in the general population, but the difference was small. The 5-year and 10-year survival rates after PEA in our study were 80% and 69%, respectively, and comparable to those at other centres.[59,60] In patients who survived the first 30 days postoperatively, the 15-year survival was 59% compared with 71% in the matched general population, and the relative survival was 83% (95% CI 60–100).

A multicentre prospective registry study that included 404 patients with newly diagnosed CTEPH from 27 centres in Europe and Canada between 2007 and 2009 reported a 3-year survival rate of 89% after PEA and in-hospital mortality rate of 4.4%.[38] The mean age at the time of surgery was 60 years. The largest PEA cohort in the world, which is from the University of California, San Diego, demonstrated a 10-year survival rate of 75% in patients who underwent PEA.[59] A total of 1410 patients were enrolled in that study between 1999 and 2010, and mean age at time of surgery was 52 years.

Papworth Hospital in Cambridge is the national referral centre for PEA in the UK and is the largest PEA centre in Europe. At that centre, 880 consecutive patients underwent PEA at a mean age of 57 years between 1997 and 2012 and had a 10-year survival rate of 72%.[60] Conditional on 3-month survival, the 5-year survival at Papworth Hospital was 92.5% for the

cohort that underwent PEA between 1997 and 2006.[96] In our study, the 5-year survival conditional on 30-day survival was similar at 86%. Aarhus University Hospital is the national centre for PEA in Denmark and has reported its long-term results for 239 patients who underwent PEA between 1994 and 2016.[85] The in-hospital mortality rate was 8.4% for the entire cohort and decreased from 22.6% in the early era to 4.3% in the later part of the study period. The 10-year survival rate was 62%. Median follow-up time was 4.4 years, and the mean age at the time of surgery was 60 years.

In *Study I* we found that relative survival was worse in women than in men. The reason for this finding is unclear, and the study was underpowered to examine sex-related differences. One of the possible explanations for women having worse relative survival could be differences in comorbidities or severity of disease at the time of diagnosis and surgery. Women might also be more susceptible to peripheral disease in the pulmonary arteries and therefore have a worse surgical outcome resulting in residual pulmonary hypertension. Previous studies have shown that patients with worse haemodynamics before surgey (i.e., higher PVR or mPAP) have an increased risk of perioperative and postoperative mortality.[52,59,97] Furthermore, the mean expected survival in Sweden was 84 years for women and 80 years for men in 2018 when the study was conducted.[98] In general, life expectancy in Sweden is long, especially for women. This impacted relative survival in our study, resulting in worse relative survival in women than in men. Women had a total relative survival of 53% (95% CI 32–73) and men had a relative survival of 76% (95% CI 54–94). In contrast with our results, a recent study from the prospective CTEPH registry demonstrated better long-term survival for women than for men at the 3-year follow-up.[62] The findings of *Study I* suggest that PEA should be first line treatment for all operable patients with CTEPH, allowing patients to have a near normal life-expectancy.

5.1.1 Limitations

Study I was a small single-centre study, and the results may not be generalizable to other centres or countries. We did not have information about post-PEA treatment, such as BPA or medical therapy. Furthermore, the study period was long, and patient care, diagnosis, and referrals may have changed during this time.

5.2 Sex and survival following PEA for CTEPH

Awareness and knowledge concerning sex-related physiological differences in the cardiovascular systems have increased, and research on this topic is becoming popular. Sex-related differences might affect symptoms, diagnosis, treatment, and ultimately the prognosis. Previous studies in CTEPH have suggested there might be differences in prognosis and survival between the sexes,[62] but no studies on sex-specific survival after surgery for CTEPH had been performed. Therefore, we conducted a Scandinavian cohort study to investigate sex-specific survival after PEA.

Study II showed that women had a higher crude early mortality rate after PEA compared with men. Long-term survival did not differ significantly between the sexes after adjustment for baseline characteristics. However, relative survival analyses indicated possible sex-related differences, given that the survival in men after PEA was close to the expected survival in a general population, while women had lower relative survival after PEA.

As previously mentioned, acute pulmonary embolism is considered to be one of the major risk factors for CTEPH, and approximately 70% of patients with CTEPH have a medical history of VTE.[18] Sex-related differences in the incidence of acute pulmonary embolism have been described in studies from Denmark, Sweden, and the US, specifically that female sex was slightly more common among incident cases (52%–53%).[8,10,99] After adjustment for age and comorbidities outcomes seemed to be similar between the sexes. However, there are differences in clinical presentation between men and women.[99-101] In an American cohort, women with acute pulmonary embolism were more likely to have normal right ventricular size on echocardiography than men.[99] Another study showed that the thrombotic burden was higher in women, and that women had more right heart dysfunction and treatment-related bleeding complications than men, but also had better survival.[102]

A study from the prospective CTEPH registry showed that the 5-year survival was better in women than in men, even though women underwent PEA less frequently.[62] That study included 679 patients, of whom half (n=339) were women. PEA was performed in 183 (54%) of these women, whereas 65% of the men in the cohort underwent PEA. Women who underwent PEA had a shorter median diagnostic delay than men, while women in the group of non-surgically treated patients had a longer median diagnostic delay than men. Microvascular disease was the most important reason for not having surgery and was more common in women (19.5%) than in men (13.5%) in the non-surgical group. Women were more likely to have high PVR or old age as contraindications to surgery. Men in the surgically treated group were more likely to have a history of coronary artery disease, and be smokers, whereas women were more likely to be obese and have thyroid disease. The proportion of women undergoing PEA was higher in high-volume centres than in low-volume centres. All-cause one-year mortality was 5.5% in women and 6.8% in men after PEA, and cardiovascular

mortality during long-term follow-up was 4.9% in women and 8.6% in men. It was not possible to analyse sex- and PEA-stratified survival in this cohort owing to the small cohort size.

In Japan, there is a 2:1 female predominance of CTEPH and a special phenotype associated with HLA-B*5021. A cohort of 150 patients was investigated to characterize the female phenotype of CTEPH in Japan.[103] Almost half of the women in the study were positive for HLA-B*5021. Women had better right ventricular function, lower right atrial pressure, and a higher cardiac index compared with men. Women were less likely to have a history of VTE but had had worse PaO2. Furthermore, women had less reduction in PVR postoperatively than men, but there was no significant difference in survival after PEA between the sexes.

Two studies have investigated sex-related differences in haemodynamic reactions in patients with CTEPH.[104,105] One study used acute vasoreactivity testing as a measure of compliance in the pulmonary vascular bed, to assess possible differences in haemodynamic reactions between the sexes, and predict the outcome in patients with CTEPH.[104] They found that both sexes had distinct haemodynamic responses and that these parameters could independently predict event-free survival. The other study used cardiopulmonary exercise testing to investigate sex-specific features in inoperable CTEPH.[105] They found different predictors for PVR in men and women. The nadir minute ventilation/carbon dioxide output was an independent predictor for PVR in men. In women, the predictor for PVR was oxygen uptake efficiency plateau. A similar study in patients with idiopathic pulmonary arterial hypertension also found sex-specific differences in predictors of PVR and cardiac output.[106]

Another study investigated sex-related differences in the right ventricle and its function in patients with idiopathic pulmonary arterial hypertension using MRI and found that men had proportionally lower right ventricular ejection fraction, lower right ventricular stroke volume, and lower left ventricular stroke volume.[107] Estimated right ventricular mass, mPAP, and PVR were similar between the sexes on MRI. The authors hypothesized that women with idiopathic pulmonary arterial hypertension have more effective adaptive remodelling of the right ventricle in response to increased afterload.

In the light of these findings, it could be possible that women have a more adaptive right ventricle and that symptoms from CTEPH arise later than in men. This could result in worse outcomes in women because of late diagnosis and therefore late treatment. High PVR has previously been identified as a negative prognostic factor for survival in CTEPH and after PEA.[59,97,108] In *Study II,* known coagulopathy and a history of VTE were more common in men, making it easier for clinicians to consider CTEPH and possibly arrive at a correct diagnosis earlier. In our cohort women were more symptomatic preoperatively, were more often medicated with phosphodiesterase inhibitors, and had more home oxygen treatment. We did not find any strong evidence to suggest that women have more severe

haemodynamics than men preoperatively, but there may still be sex-specific differences in the timing of surgery. However, there was no evidence of women having inferior surgical results that could explain the higher crude early mortality rate in women.

5.2.1 Limitations

In *Study II* we lacked information on post-PEA treatment, such as medical therapy or BPA. It was also unknown whether warfarin or NOACs were used as anticoagulation. We had no information on non-surgically treated patients with CTEPH, nor on time from onset of symptoms to diagnosis and surgery. Moreover, our study period spanned nearly 30 years, and patient care has evolved during this time.

5.3 Association of residual pulmonary hypertension with survival after PEA for CTEPH

In *Study III* we found a significant and clinically relevant association between early postoperative mPAP ≥30 mmHg and long-term survival after PEA for CTEPH. This association remained after accounting for preoperative differences in baseline characteristics, including preoperative mPAP, and after excluding patients who survived for less than 30 days after PEA. Previous studies have shown that persistent or residual pulmonary hypertension (PH) immediately following PEA increases the risk of in-hospital death.[52,97] Our findings add to the previous knowledge because they suggest that early mPAP ≥30 mmHg is relevant to the prognosis also in patients who survive beyond the early postoperative phase.

Previous studies have reported conflicting results regarding the relationship between early postoperative pulmonary haemodynamics and long-term survival.[38,60,97,109-112] Comparing studies directly with each other is difficult because the definition of persisting or residual PH after PEA varies from study to study. Furthermore, measurements were obtained at various timepoints after surgery (e.g., postoperative days 1–3, or 3–6 months after surgery). Different criteria have been used to define persistent or residual PH after PEA, with some studies using definitions based on mPAP,[38,60,110,111] others using PVR,[97,112] and one a combination of both.[109]

5.3.1 Residual pulmonary hypertension and early mortality after PEA

Patients with high PVR post-PEA, as a sign of residual PH, have been shown to have a higher risk of in-hospital mortality. Results from the San Diego cohort of 1500 patients were reported by Jamieson et al.[52] and showed that patients with postoperative PVR >500 dynes•s•cm^{-5} had a mortality rate of 30%. Similar results for in-hospital mortality in 2700 patients from the San Diego cohort were later reported by Madani et al.[59]

5.3.2 Residual pulmonary hypertension—not related to long-term outcome?

In a study by Freed et al., the effect of residual PH, defined as mPAP ≥30 mmHg at the 3-month follow-up after PEA, on long-term survival was assessed in 314 patients who survived to discharge.[110] At the 3-month follow-up patients with mPAP <30 mmHg had better exercise capacity, more improved symptoms, and were less likely to be on medication for PH; however, there was no difference in long-term survival between the two groups. The mean follow-up time in that study was 4.2 years. In another study from the UK persistent PH was defined as mPAP ≥25 mmHg and PVR ≥240 dynes•s•cm^{-5} at 3 months after PEA.[109] PEA was performed in 236 patients and 198 survived to discharge. Three months postoperatively 162 patients underwent repeat RHC. There was no significant difference in survival between the groups with persistent PH compared with patients without persistent PH 3 years after PEA. The results were similar in a single-centre study that included 499 patients who undwent PEA between 1995 and 2014. Residual PH was defined as mPAP ≥25 mmHg

measured within 48 h of PEA and 34% had residual PH immediately postoperatively.[111] The prognosis for patients with residual PH was poorer, but there was no significant difference in long-term survival between the groups after excluding in-hospital mortality.

5.3.3 Residual pulmonary hypertension—a prognostic marker for worse survival

In contrast, many studies have identified a correlation between residual PH and worse survival.[38,60,112] A report from the United Kingdom National Cohort, that included 880 patients enrolled between 1997 and 2012, showed that patients with residual PH had worse long-term survival.[60] The threshold for worse survival and increased risk of CTEPH-related death was mPAP ≥38 mmHg measured 3–6 months post-PEA. The correlation between mPAP measured on day 1 and that measured 3–6 months after PEA was only moderate. The long-term outcome was better predicted by mPAP measured at 3–6 months postoperatively than by early postoperative pulmonary haemodynamics.

In a study from Vienna, the strongest independent predictor of long-term survival or freedom from lung transplantation was the PVR immediately after PEA. All 110 patients who underwent PEA in Vienna between 1994 and 2010 were included in the study.[112] Immediate postoperative PVR measurements were obtained within 4 days of surgery.

In a study from the International Prospective CTEPH registry that included 404 preoperative PEA patients between 2007 and 2009,[38] the limits for residual postoperative PH were defined as mPAP ≥25 mmHg by RHC or systolic pulmonary artery pressure ≥40 mmHg using echocardiography. Measurements were obtained 2–3 days postoperatively. The mortality rate in patients with residual PH was significantly increased 3–5 years postoperatively.

There are many indications suggesting that both preoperative and postoperative pulmonary haemodynamics affect long-term patient outcomes and survival after PEA. To improve haemodynamics in the pulmonary circulation, the pulmonary arteries have to be cleared of obstructions formed by fibrotic material and scar tissue, and the most effective treatment to date is PEA.[113] Two possible mechanisms for a very early postoperative mPAP ≥30 mmHg are incomplete surgical endarterectomy or presence of distal microvascular disease. However, other factors may also be relevant in the very early postoperative phase. According to a meta-analysis, residual PH was found in 25% of patients who underwent PEA, but this estimate must be interpreted with caution because there is no generally accepted definition of residual PH post-PEA.[114] The European Respiratory Society recently published a statement on PEA and CTEPH, which declared that residual PH is the most common cause of in-hospital mortality after PEA and is challenging to treat in the early postoperative period.[115] ECMO may be necessary for short-term mechanical circulatory support to survive the early postoperative phase. It is also important to pay attention to patients who develop symptoms after discharge, given that they could be candidates for medical treatment or BPA.[56]

5.3.4 Summary of residual pulmonary hypertension

Study III, together with previous reports, clearly indicates that the risk of mortality is higher in patients with elevated mPAP early after surgery. However, the precise definition of residual PH following PEA for CTEPH remains a matter of debate. There are benefits in using fixed values (e.g., a mPAP of 30 mmHg) to define residual PH after PEA, in terms of facilitating decision-making and having a measurement that is easily obtained. The optimal cut-off value is still to be found, and careful interpretation is necessary as long as an arbitrarily chosen cut-off value is used. It is likely that if a patient falls just below the cut-off value, the prognosis is probably very similar to that of another patient who is just above the cut-off.

Previous studies have consistently shown that patients with residual PH have worse short-term outcomes, but the results regarding long-term outcomes have been conflicting. Our current study findings are comparable to those two recent influential studies from the United Kingdom National Cohort and the International Prospective CTEPH Registry.[38,60] Together, these studies demonstrate that early postoperative pulmonary hemodynamics are important for the long-term prognosis. Therefore, clinicians should follow patients with residual PH closely to intervene and possibly improve their long-term prognosis.

In conclusion, *Study III* found a strong and clinically relevant association of residual PH with long-term survival after PEA for CTEPH. According to our results, early mPAP ≥30 mmHg is relevant in terms of prognosis, and the survival difference between the groups at long-term follow-up is clinically relevant. Patients with residual PH need careful surveillance to improve their clinical outcomes. Measurements of mPAP obtained early after PEA in the intensive care unit may contribute to prognostication.

5.3.5 Limitations

In this study, there was no standardized protocol for obtaining measurements of early mPAP. The mPAP data were collected from patient charts, and there was variability in timing and procedure. Moreover, information on patient fluid status and use of vasoactive drugs was unavailable. We did not have information on postoperative targeted medication, BPA, or anticoagulation strategies. These factors probably also affect the long-term prognosis. The 30-year study period could have affected our results because of changes in diagnosis, referral patterns, and patient care, including perioperative management and medical treatment.

5.4 Quality of life and functional status after PEA

For many years, medical research has focused on hard outcome measures such as mortality or mean pulmonary artery pressure. Patient-reported outcome measures are becoming increasingly popular, but the results might be complex to interpret. In *Study IV* we wanted a broad description of our study population and therefore used various instruments for QoL as well as functional status.

In *Study IV* QoL measured after PEA using the validated RAND-36 instrument was close to the expected in an age-matched general population in Sweden, and CAMPHOR scores were low and comparable to those observed in a large UK cohort of patients with CTPEH following PEA. Functional status according to KPS indicated that three quarters of study participants were able to conduct normal activities at late follow-up without the need for specialized care. The 6MWD late after PEA showed some improvement when compared to the preoperative distance.

More information on health related QoL following PEA for CTEPH is needed. A recent review found that QoL was worse in patients with CTEPH than in a healthy population.[116] Furthermore, QoL improved significantly after PEA; however, more studies are needed to validate appropriate instruments for measurement of QoL in the CTEPH and PEA populations. It was also noted in the review, that CAMPHOR is the only validated QoL instrument specifically for PH and that comparing different studies is difficult because of use of different QoL instruments.

5.4.1 Quality of life after PEA

The first study of QoL in patients undergoing PEA was reported by the San Diego group in 1999.[117] In this cross-sectional study consisted of 514 patients who underwent PEA between 1970 and 1994 and survived to be discharged. Of these patients, 123 were lost to follow-up, 51 had died, 14 were excluded because of language difficulties, and 3 patients were excluded for undergoing lung transplantation, leaving 308 patients for inclusion in the study. The median time from PEA to survey was 2.3 years (range 1–16). The mean age at the time of the study was 56.2 years (range 19–89). The RAND-36 response rate was 97% (298/308). Post-PEA patients rated their QoL slightly below that of healthy individuals in the US. Results from RAND-36 were considerably better for patients after PEA, than in a separate group of pre-PEA patients.

A Japanese study investigated QoL with the SF-36 before and after invasive treatment for CTEPH.[118] Thirty-nine patients were included, of whom 15 were treated by PEA and 24 by BPA. There were significant differences in baseline characteristics and follow-up durations between the PEA and BPA groups. The patients in the PEA group had higher mPAP and

PVR and lower exercise tolerance than those in the BPA group. The mean follow-up time was 4.4 months in the PEA group and 7.9 months in the BPA group. Haemodynamic improvement was seen in the PEA group, with a reduction in mean mPAP from 43 mmHg to 25 mmHg and an increase in the mean cardiac index from 1.8 l/min/m^2 to 2.3 l/min/m^2. In both treatment groups, the SF-36 scores were lower than the national average in Japan. There was no significant difference in improvement of QoL between the treatment groups. However, there was significant improvement in the QoL domains of physical functioning, general health, vitality, and mental health in PEA group.

Another study reported outcomes after PEA for 128 patients, including QoL measured by the SF-36 at the 3-year follow-up.[119] The majority of the patients (67%) were men, the mean age was 51 years, and the response rate at 3 years postoperatively was 84%. The 1-year and 3-year survival rates were 91% and 90%, respectively. During follow-up, the mean mPAP decreased from 47 mmHg to 28 mmHg and the mean cardiac index improved from 1.9 l/min/m^2 to 2.9 l/min/m^2. QoL measured by the SF-36 improved considerably, with increases in both physical (32 to 46) and mental (38 to 50) component summary scores.

The haemodynamic improvement after PEA was similar in all the three above-mentioned studies.[117-119] The patients in two of the studies had a similar mean age of approximately 60 years,[117,118] whereas those in the third study were younger, with a mean age of 51 years.[119] The QoL experienced by patients is likely affected by age. We compared the QoL data in *Study IV* with those in an age-matched general population in Sweden[120] and found the RAND-36 scores to be similar, except for physical functioning and role physical domain scores, which were slightly lower than in the general reference population. The results for RAND-36 in *Study IV* were thus in line with those in the San Diego group.[117] Interestingly, the Japanese SF-36 scores were low across all domains.[118] One plausible explanation could be the differences in time from surgery to follow-up. The follow-up time in the Japanese study was short (4 months), whereas the remaining studies had longer mean follow-up durations of approximately 3 years. Convalescence after open heart surgery takes 2–3 months in uncomplicated cases but recovery can take up to a year in complex cases. Comparison of the studies measuring QoL postoperatively by RAND-36 or SF-36 is shown in Figure 15.

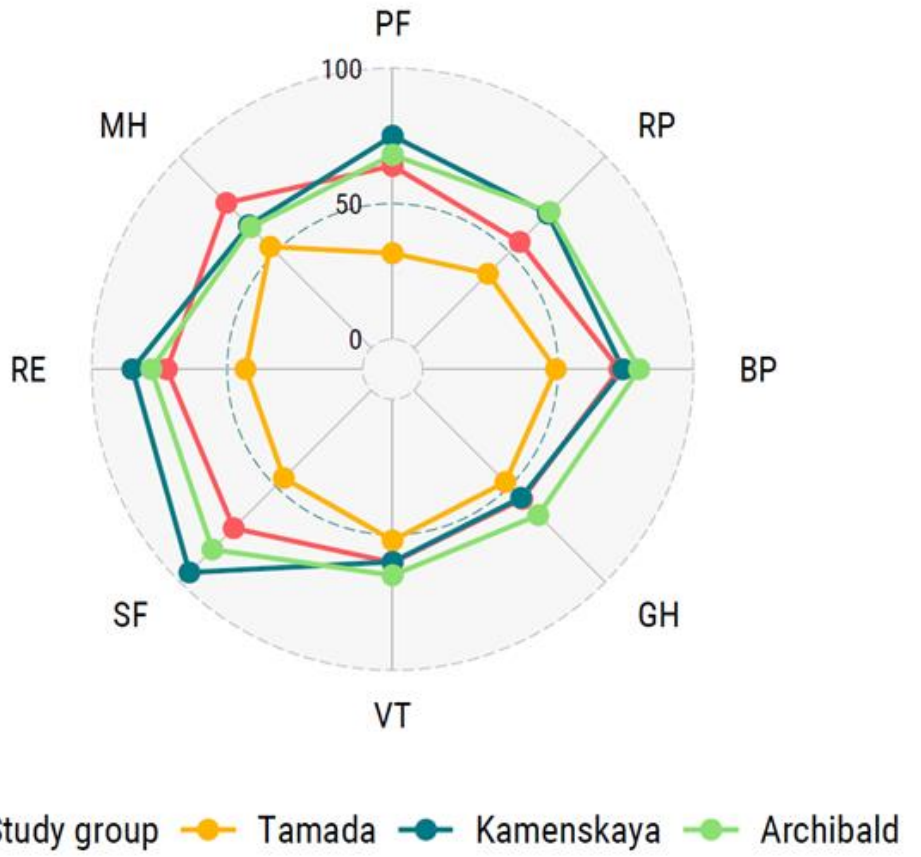


Figure 15. *Comparison of postoperative RAND-36 scores obtained in our study (red) compared with those in three other studies.*[117-119] *BP, bodily pain; GH, general health; ME, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.*

The most extensive study of patient-reported outcomes and QoL after PEA was conducted in the UK. The cohort consisted of 1324 patients who underwent surgery between 2006 and 2017.[66] Significant haemodynamic improvement was seen at the 1-year follow-up, mean mPAP was reduced from 45 mmHg to 25 mmHg and the mean cardiac index improved from 2.2 l/min/m^2 to 2.3 l/min/m^2. Patient-reported outcomes were assessed by the CAMPHOR before PEA and annually for up to 5 years after PEA. One year after PEA, CAMPHOR scores were available for 784 patients (60%), but the number of patients with available data declined year by year thereafter. The CAMPHOR score improved significantly across all domains postoperatively. The median CAMPHOR scores 5 years after PEA were 4 for activity, 2 for QoL, and 3 for symptoms. Improvement in CAMPHOR scores were greater in patients with no residual PH (defined as post-PEA mPAP <30 mmHg) than in those with residual PH (mPAP ≥30 mmHg). The CAMPHOR scores were also compared to a propensity score matched CTEPH population that did not undergo surgery, and the post-PEA population had significantly better CAMPHOR scores at follow-up. In our study, CAMPHOR scores were obtained at a mean of 5.9 years (range 0.4–20) after PEA and were comparable with those in

the UK cohort.[66] This finding suggests that the improvement in QoL after PEA can be sustained beyond 5 years and that some patients achieve lifelong improvement. However, the improvement in QoL during long-term follow-up might reflect positive selection bias in the survivor group. Moreover, cultural differences in the perception of health and illness may have affected answers concerning patient-reported outcomes.

5.4.2 Functional status after PEA

The San Diego group used "self-estimated" postoperative NYHA functional class to evaluate functional status in their cohort. Two years after PEA, a majority of patients (93%) categorized themselves as NYHA class I–II.[117] In the UK cohort, a clear improvement in functional status was detected, with 88% of patients reported to be in WHO functional class III–IV preoperatively and 73% to be in WHO functional class I–II by one year postoperatively.[66] A previous study demonstrated a correlation between NYHA functional class and KPS and indicated that categories of functional status were better discriminated by KPS than by NYHA functional class.[81] Even if KPS is rarely used in cardiovascular research, it is a robust measurement and it is intuitive to interpret and understand. KPS may also be better than NYHA functional class for describing clinically meaningful deterioration in patients, especially at lower levels of performance.[81]

A recent single-centre study compared haemodynamics and functional status between patients who underwent PEA and BPA.[121] Patients were evaluated preoperatively and 5 months after procedure. Improvement in functional status measured by cardiopulmonary exercise test was similar in both groups at follow-up. Both groups showed improvement in haemodynamics, but the PEA group had slightly more improvement in PVR and mPAP. The mean mPAP decreased from 46 mmHg to 28 mmHg in the group treated by PEA. The 30-day mortality was 4.8% in the PEA group. Preoperatively 81% of patients undergoing PEA were in NYHA class III–IV, and postoperatively 74% of the PEA patients were in NYHA class I–II, and none in NYHA class IV.

In *Study IV,* functional status was assessed using KPS at late follow-up after PEA for CTEPH. All study participants were able to live at home and care for most personal needs, and 74% were able to conduct normal activities without need of specialized care. Furthermore, one third of patients reported a KPS score of 100% (i.e., normal life, no complaints, and no evidence of disease). Previous studies have showed similar patterns of improvement in 6MWD after PEA.[66,118] The UK cohort reported an increase in mean 6MWD from 309 m preoperatively to 366 m one year after PEA.[66] In the study from Japan, the mean 6MWD improved from 281 m preoperatively to 372 m after PEA, but the improvement was not statistically significant.[118] In another study, the minimal clinically important difference in 6MWD in patients with pulmonary arterial hypertension was approximately 33 m.[77] In *Study IV,* the mean 6MWD improved by 32 m, but was not statistically significant; however, this

might still represent a clinically meaningful improvement in functional capacity. Previous research has shown that improvement in 6MWD could be expected for up to 2 years after PEA and is likely to be sustained for up to 5 years after surgery.[122] It is still unclear, if this improvement can be sustained in the long-term or if there is a natural age-related decline.

5.4.3 Limitations

Study IV was a small single-centre study and spanned over a long study period of nearly three decades. Patient care has progressed during this time, and new treatment modalities, such as medical therapy for PH and BPA have emerged. Data on post-PEA treatment such as BPA or medication for PH were not available.

There was wide variation in the follow-up times for all measurements because of the cross-sectional study design. We did not have baseline (i.e., pre-PEA) RAND-36 or CAMPHOR data and only a subset of the study population had RHC data available late after PEA.

Of all the living patients in our cohort, 74% participated in the cross-sectional evaluation of QoL by RAND-36. Some patients did not respond even after reminders by post and telephone. We can only speculate about the reasons for patients declining to participate; whether these patients were feeling well and therefore unwilling to take the time to participate or if they were too ill to answer is unknown.

Finally, the results of *Study IV* may have been affected by the COVID-19 pandemic. Patients with CTEPH are considered to be high risk for COVID-19. A few patients included notes in the RAND-36 questionnaires reporting that they felt physically restrained because of strict self-quarantine during the pandemic. Data for *Study IV* were collected during 2020 before vaccines were available.

6 Conclusions

Study I Life expectancy following PEA was shorter than in the general population. The difference was small in those who survived the operation and the early postoperative period. Patients with CTEPH, who are surgical candidates should undergo PEA to improve prognosis.

Study II The crude early mortality rate was higher in women who underwent PEA for CTEPH than in their male counterparts. After adjustment for differences in baseline characteristics, there was no significant sex-related difference in long-term survival. Relative survival suggested that the observed survival in men was close to the expected survival in the matched general population, whereas survival in women deviated notably from that in the matched general population.

Study III Residual PH had a strong and clinically relevant association with long-term survival after PEA for CTEPH. After adjustments for differences in baseline characteristics, the absolute survival difference during long-term follow-up was clinically meaningful and implies a need for careful surveillance to improve clinical outcomes in patients with residual PH. Early postoperative RHC measurements of mPAP seem to be helpful for prognostication following PEA for CTEPH.

Study IV QoL after PEA approached that in a reference population. CAMPHOR scores after PEA were comparable to those in a large UK cohort. Functional status improved slightly when assessed late after PEA, and three-quarters of the study population were able to conduct normal activities at late follow-up without the need for specialized care. Our findings suggest that many patients had satisfactory QoL and high functional status late after PEA.

7 Future perspectives

CTEPH is a very rare disease that is not widely known to non-specialist clinicians. Research on CTEPH and PEA has been challenging owing to small numbers of patients, and there are many knowledge gaps yet to be filled.

There is a need for more basic research on CTEPH. The pathophysiology of CTEPH is complex and not yet fully understood. The mechanisms that initiate development of CTEPH remain a mystery. Why do some patients develop CTEPH after acute pulmonary embolism while others do not? Identification of the mechanisms behind this phenomenon could offer a solution to the dream scenario, namely, prevention of CTEPH. Better knowledge about the disease mechanism could also offer possibilities for development of new medication.

In this Scandinavian cohort, we found that men had a near normal life expectancy after PEA. Women, however, had worse relative survival. More research is needed to confirm these results and find possible mechanisms behind this to improve prognosis for women. We also found that women had higher crude early mortality after PEA. More research on the right ventricle and its function would be useful to uncover if there are sex-related differences in right heart physiology and how this could affect symptoms, treatment, and prognosis in patients with CTEPH.

We found that early residual PH after PEA was associated with worse long-term prognosis (residual PH defined as mPAP ≥30 mmHg); however, more studies are needed to find the optimal method and cut-off values for the definition of residual PH after PEA to improve prognosis for those patients with residual postoperative PH.

The new treatment modalities BPA and medical therapy require further assessment and comparison to PEA to find the optimal treatment for each patient with CTEPH based on haemodynamic profile, surgical risk, and patient preference.

Prospective and up-to-date studies on QoL and functional status are needed to further describe the population of CTEPH and PEA patients. As previously mentioned, research in this field has mostly focused on survival and haemodynamic results. Relevant comparisons on QoL and functional status would provide useful information about expectations after PEA.

8 Acknowledgements

I wish to express my sincere gratitude to:

Professor *Ulrik Sartipy*, for simply being the best supervisor, colleague, and mentor

Associate professor *Matthias Corbascio*, co-supervisor; for dedication, insights, and support

Professor *Anders Franco-Cereceda* for seeing the potential in me and creating a research friendly environment

Co-authors

Susanne Hylander for helping with patient interviews

The SPAHR steering committee for providing data

Associate professor *Peter Svenarud*, head of the Department of Cardiothoracic Surgery, for creating the great clinical working atmosphere

All colleagues at the Department of Cardiothoracic Surgery at Karolinska University Hospital

Family and friends for support

This work was supported by:

The Swedish Heart-Lung Foundation, the Åke Wiberg Foundation, Region Stockholm (ALF project), Karolinska Institutet Foundations and Funds, and the Swedish Association for Cardiothoracic Surgery (the Senning award)

9 References

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43:3618-3731.

2. Swedish Pulmonary Artery Hypertension & CTEPH Registry. SPAHR Annual Report 2021. https://www.ucr.uu.se/spahr/arsrapporter/arsrapport-2021/viewdocument/155. 2022.

3. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jimenez D, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41:543-603.

4. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med*. 2004;350:2257-2264.

5. Ljungdahl M. Gibt es eine chronische Embolisierung der Lungenarterie. *Dtsch Arch klin med*. 1928;160:1.

6. Hollister LE, Cull VL. The syndrome of chronic thrombosis of the major pulmonary arteries. *Am J Med*. 1956;21:312-320.

7. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation*. 2011;124:1973-1981.

8. Lehnert P, Lange T, Møller CH, Olsen PS, Carlsen J. Acute Pulmonary Embolism in a National Danish Cohort: Increasing Incidence and Decreasing Mortality. *Thromb Haemost*. 2018;118:539-546.

9. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. *Am J Med*. 2013;126:832.e813-821.

10. Andersson T, Söderberg S. Incidence of acute pulmonary embolism, related comorbidities and survival; analysis of a Swedish national cohort. *BMC Cardiovasc Disord*. 2017;17:155.

11. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Huisman MV. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. *Haematologica*. 2010;95:970-975.

12. Becattini C, Agnelli G, Pesavento R, Silingardi M, Poggio R, Taliani MR, Ageno W. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. *Chest*. 2006;130:172-175.

13. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, Delcroix M, Pruszczyk P, Mairuhu AT, Huisman MV, Klok FA. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49.

14. Yu Y, Yang L, Zhang Y, Dong L, Xia J, Zhu N, Han X, Fang L, Chai Y, Niu M, et al. Incidence and risk factors of chronic thromboembolic pulmonary hypertension in patients with diagnosis of pulmonary embolism for the first time in real world. *Clin Respir J*. 2018;12:2551-2558.

15. Swedish Pulmonary Artery Hypertension & CTEPH Registry. Swedish Pulmonary Artery Hypertension & CTEPH Registry. https://www.ucr.uu.se/spahr/om-spahr. 2019. Accessed 2019-12-19.

16. Valerio L, Mavromanoli AC, Barco S, Abele C, Becker D, Bruch L, Ewert R, Faehling M, Fistera D, Gerhardt F, et al. Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study. *Eur Heart J*. 2022;43:3387-3398.

17. Papamatheakis DG, Poch DS, Fernandes TM, Kerr KM, Kim NH, Fedullo PF. Chronic Thromboembolic Pulmonary Hypertension: JACC Focus Seminar. *J Am Coll Cardiol*. 2020;76:2155-2169.

18. Bonderman D, Wilkens H, Wakounig S, Schäfers HJ, Jansa P, Lindner J, Simkova I, Martischnig AM, Dudczak J, Sadushi R, et al. Risk factors for chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2009;33:325-331.

19. Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2011;364:351-360.

20. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. *Circulation*. 1999;99:1325-1330.

21. Yan L, Li X, Liu Z, Zhao Z, Luo Q, Zhao Q, Jin Q, Yu X, Zhang Y. Research progress on the pathogenesis of CTEPH. *Heart Fail Rev*. 2019;24:1031-1040.

22. Klok FA, Dzikowska-Diduch O, Kostrubiec M, Vliegen HW, Pruszczyk P, Hasenfuß G, Huisman MV, Konstantinides S, Lankeit M. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost*. 2016;14:121-128.

23. Matthews DT, Hemnes AR. Current concepts in the pathogenesis of chronic thromboembolic pulmonary hypertension. *Pulm Circ*. 2016;6:145-154.

24. Dorfmuller P, Gunther S, Ghigna MR, Thomas de Montpreville V, Boulate D, Paul JF, Jais X, Decante B, Simonneau G, Dartevelle P, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. *Eur Respir J*. 2014;44:1275-1288.

25. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67-119.

26. Harjola VP, Mebazaa A, Čelutkienė J, Bettex D, Bueno H, Chioncel O, Crespo-Leiro MG, Falk V, Filippatos G, Gibbs S, et al. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18:226-241.

27. Houston BA, Brittain EL, Tedford RJ. Right Ventricular Failure. *N Engl J Med*. 2023;388:1111-1125.

28. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685-713.

29. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, Al-Nahhas A. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med*. 2007;48:680-684.

30. Kharat A, Hachulla AL, Noble S, Lador F. Modern diagnosis of chronic thromboembolic pulmonary hypertension. *Thromb Res*. 2018;163:260-265.

31. van Kan C, van der Plas MN, Reesink HJ, van Steenwijk RP, Kloek JJ, Tepaske R, Bonta PI, Bresser P. Hemodynamic and ventilatory responses during exercise in chronic thromboembolic disease. *J Thorac Cardiovasc Surg*. 2016;152:763-771.

32. Sugiura T, Tanabe N, Matsuura Y, Shigeta A, Kawata N, Jujo T, Yanagawa N, Sakao S, Kasahara Y, Tatsumi K. Role of 320-slice CT imaging in the diagnostic workup of patients with chronic thromboembolic pulmonary hypertension. *Chest*. 2013;143:1070-1077.

33. Rogberg AN, Gopalan D, Westerlund E, Lindholm P. Do radiologists detect chronic thromboembolic disease on computed tomography? *Acta Radiol*. 2019;60:1576-1583.

34. Grosse A, Grosse C, Lang IM. Distinguishing Chronic Thromboembolic Pulmonary Hypertension From Other Causes of Pulmonary Hypertension Using CT. *AJR Am J Roentgenol*. 2017;209:1228-1238.

35. Bunclark K, Newnham M, Chiu YD, Ruggiero A, Villar SS, Cannon JE, Coghlan G, Corris PA, Howard L, Jenkins D, et al. A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension. *J Thromb Haemost*. 2020;18:114-122.

36. Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, Vidal X, Riera-Mestre A, Castro-Salomó A, Cuquet-Pedragosa J, Ortiz-Santamaria V, Mauri-Plana M, Solé C, et al. Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome: A Randomized Noninferiority Trial. *Ann Intern Med*. 2019;171:685-694.

37. Duffett L, Carrier M. Inferior vena cava filters. *J Thromb Haemost*. 2017;15:3-12.

38. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, et al. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. *Circulation*. 2016;133:859-871.

39. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv*. 2012;5:748-755.

40. Tanabe N, Kawakami T, Satoh T, Matsubara H, Nakanishi N, Ogino H, Tamura Y, Tsujino I, Ogawa A, Sakao S, et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: A systematic review. *Respir Investig*. 2018;56:332-341.

41. Ghofrani HA, Humbert M, Langleben D, Schermuly R, Stasch JP, Wilkins MR, Klinger JR. Riociguat: Mode of Action and Clinical Development in Pulmonary Hypertension. *Chest*. 2017;151:468-480.

42. Ghofrani HA, Galie N, Grimminger F, Grunig E, Humbert M, Jing ZC, Keogh AM, Langleben D, Kilama MO, Fritsch A, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2013;369:330-340.

43. Ghofrani HA, Simonneau G, D'Armini AM, Fedullo P, Howard LS, Jaïs X, Jenkins DP, Jing ZC, Madani MM, Martin N, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir Med*. 2017;5:785-794.

44. Sadushi-Kolici R, Jansa P, Kopec G, Torbicki A, Skoro-Sajer N, Campean IA, Halank M, Simkova I, Karlocai K, Steringer-Mascherbauer R, et al. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. *Lancet Respir Med*. 2019;7:239-248.

45. Hill JD. John H. Gibbon, Jr. Part I. The development of the first successful heart-lung machine. *Ann Thorac Surg*. 1982;34:337-341.

46. Senning A. Developments in cardiac surgery in Stockholm during the mid and late 1950s. *J Thorac Cardiovasc Surg*. 1989;98:825-832.

47. Radegran K. The early history of cardiac surgery in Stockholm. *J Card Surg*. 2003;18:564-572.

48. Matthews AM. The development of the Starr-Edwards heart valve. *Tex Heart Inst J*. 1998;25:282-293.

49. Moser KM, Rhodes PG, Hufnagel CC. Chronic unilateral pulmonary-artery thrombosis: Successful thrombendarterectomy with thirty-month follow-up observation *N Engl J Med*. 1965;272:1195-1199.

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

51. Jamieson SW, Auger WR, Fedullo PF, Channick RN, Kriett JM, Tarazi RY, Moser KM. Experience and results with 150 pulmonary thromboendarterectomy operations over a 29-month period. *J Thorac Cardiovasc Surg*. 1993;106:116-126.

52. 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;76:1457-1462.

53. Madani MM. Surgical Treatment of Chronic Thromboembolic Pulmonary Hypertension: Pulmonary Thromboendarterectomy. *Methodist Debakey Cardiovasc J*. 2016;12:213-218.

54. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev*. 2017;26.

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

56. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53.

57. Moser KM, Metersky ML, Auger WR, Fedullo PF. Resolution of vascular steal after pulmonary thromboendarterectomy. *Chest*. 1993;104:1441-1444.

58. Banks DA, Pretorius GV, Kerr KM, Manecke GR. Pulmonary endarterectomy: Part II. Operation, anesthetic management, and postoperative care. *Semin Cardiothorac Vasc Anesth*. 2014;18:331-340.

59. 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;94:97-103.

60. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, Treacy C, Ponnaberanam A, Condliffe R, Sheares K, et al. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. *Circulation*. 2016;133:1761-1771.

61. Quadery SR, Swift AJ, Billings CG, Thompson AAR, Elliot CA, Hurdman J, Charalampopoulos A, Sabroe I, Armstrong IJ, Hamilton N, et al. The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2018;52.

62. Barco S, Klok FA, Konstantinides SV, Dartevelle P, Fadel E, Jenkins D, Kim NH, Madani M, Matsubara H, Mayer E, et al. Sex-specific differences in chronic

thromboembolic pulmonary hypertension. Results from the European CTEPH registry. *J Thromb Haemost*. 2020;18:151-161.

63. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10:407-415.

64. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res*. 2006;15:103-115.

65. Selimovic N, Rundqvist B, Kjork E, Viriden J, Twiss J, McKenna SP. Adaptation and validation of the Cambridge pulmonary hypertension outcome review for Sweden. *Scand J Public Health*. 2012;40:777-783.

66. Newnham M, Bunclark K, Abraham N, Ali S, Amaral-Almeida L, Cannon JE, Doughty N, Ng C, Ponnaberanam A, Sheares K, et al. CAMPHOR score: patient-reported outcomes are improved by pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2020;56.

67. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ*. 2002;324:1417.

68. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med*. 2001;33:350-357.

69. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics*. 1999;15:141-155.

70. Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, Gaine S. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43:40s-47s.

71. Taichman DB, McGoon MD, Harhay MO, Archer-Chicko C, Sager JS, Murugappan M, Chakinali MM, Palevsky HI, Gallop R. Wide variation in clinicians' assessment of New York Heart Association/World Health Organization functional class in patients with pulmonary arterial hypertension. *Mayo Clin Proc*. 2009;84:586-592.

72. Balke B. A simple field test for the assessment of physical fitness. REP 63-6. *Rep Civ Aeromed Res Inst US*. 1963:1-8.

73. Camarri B, Eastwood PR, Cecins NM, Thompson PJ, Jenkins S. Six minute walk distance in healthy subjects aged 55-75 years. *Respir Med*. 2006;100:658-665.

74. Cazzoletti L, Zanolin ME, Dorelli G, Ferrari P, Dalle Carbonare LG, Crisafulli E, Alemayohu MA, Olivieri M, Verlato G, Ferrari M. Six-minute walk distance in healthy subjects: reference standards from a general population sample. *Respir Res*. 2022;23:83.

75. Zou H, Zhu X, Zhang J, Wang Y, Wu X, Liu F, Xie X, Chen X. Reference equations for the six-minute walk distance in the healthy Chinese population aged 18-59 years. *PLoS One*. 2017;12:e0184669.

76. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166:111-117.

77. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2012;186:428-433.

78. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract*. 2017;23:377-381.

79. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. *Cancer*. 1948;1:634-656.

80. Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. *BMC Med Inform Decis Mak*. 2013;13:72.

81. Johnson MJ, Bland JM, Davidson PM, Newton PJ, Oxberry SG, Abernethy AP, Currow DC. The relationship between two performance scales: New York Heart Association Classification and Karnofsky Performance Status Scale. *J Pain Symptom Manage*. 2014;47:652-658.

82. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-349.

83. Vikholm P, Ivert T, Nilsson J, Holmgren A, Freter W, Ternström L, Ghaidan H, Sartipy U, Olsson C, Granfeldt H, et al. Validity of the Swedish Cardiac Surgery Registry. *Interact Cardiovasc Thorac Surg*. 2018;27:67-74.

84. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24:659-667.

85. Korsholm K, Andersen A, Mellemkjaer S, Nielsen DV, Klaaborg KE, Ilkjaer LB, Nielsen-Kudsk JE. Results from more than 20 years of surgical pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension in Denmark. *Eur J Cardiothorac Surg*. 2017;52:704-709.

86. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541-549.

87. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart*. 2010;96:1617-1621.

88. Swedish Pulmonary Arterial Hypertension Registry. SPAHR Annual Report 2020. https://www.ucr.uu.se/spahr/arsrapporter. 2021.

89. Dickman PW, Coviello E. Estimating and Modeling Relative Survival. 2015;15:186-215.

90. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. 2011;46:399-424.

91. Imai K, Ratkovic M. Covariate balancing propensity score. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. 2014;76:243-263.

92. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661-3679.

93. Royston P, Lambert PC. *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model*. Stata Press; 2011.

94. Lambert PC, Royston P. Further Development of Flexible Parametric Models for Survival Analysis. *The Stata Journal*. 2009;9:265-290.

95. Kim SH, Lee JW, Ahn JM, Kim DH, Song JM, Lee SD, Lee JS. Long-term outcomes of surgery for chronic thromboembolic pulmonary hypertension compared with medical therapy at a single Korean center. *Korean J Intern Med*. 2017;32:855-864.

96. Freed DH, Thomson BM, Tsui SS, Dunning JJ, Sheares KK, Pepke-Zaba J, Jenkins DP. Functional and haemodynamic outcome 1 year after pulmonary thromboendarterectomy. *Eur J Cardiothorac Surg*. 2008;34:525-529.

97. Mayer E, Jenkins D, Lindner J, D'Armini A, Kloek J, Meyns B, Ilkjaer LB, Klepetko W, Delcroix M, Lang I, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *J Thorac Cardiovasc Surg*. 2011;141:702-710.

98. Statistics Sweden. Mean survival in Sweden 2018. https://www.scb.se/hitta-statistik/sverige-i-siffror/manniskorna-i-sverige/medellivslangd-i-sverige/. 2019.

99. Pribish AM, Beyer SE, Krawisz AK, Weinberg I, Carroll BJ, Secemsky EA. Sex differences in presentation, management, and outcomes among patients hospitalized with acute pulmonary embolism. *Vasc Med*. 2020;25:541-548.

100. Tanabe Y, Yamamoto T, Murata T, Mabuchi K, Hara N, Mizuno A, Nozato T, Hisatake S, Obayashi T, Takayama M, et al. Gender Differences Among Patients With Acute Pulmonary Embolism. *Am J Cardiol*. 2018;122:1079-1084.

101. Barrios D, Morillo R, Guerassimova I, Barbero E, Escobar-Morreale H, Cohen AT, Becattini C, Tapson V, Yusen R, Jimenez D. Sex differences in the characteristics and short-term prognosis of patients presenting with acute symptomatic pulmonary embolism. *PLoS One*. 2017;12:e0187648.

102. Panigada G, Masotti L, Rosi C, Teghini L, Cimolato B, Bertieri MC, Angotti C, Romagnoli AM, Cascinelli I, De Crescenzo V, et al. Thromboembolic burden, prognostic assessment and outcomes of females compared to males in acute pulmonary embolism. *Acta Clin Belg*. 2016;71:142-148.

103. Shigeta A, Tanabe N, Shimizu H, Hoshino S, Maruoka M, Sakao S, Tada Y, Kasahara Y, Takiguchi Y, Tatsumi K, et al. Gender differences in chronic thromboembolic pulmonary hypertension in Japan. *Circ J*. 2008;72:2069-2074.

104. Yang YL, Yu YZ, Yuan P, Gong SG, Wang CY, Li Y, Zhao QH, Jiang R, Wu WH, He J, et al. Sex differences of hemodynamics during acute vasoreactivity testing to predict the outcomes of chronic thromboembolic pulmonary hypertension. *Clin Respir J*. 2020;14:611-621.

105. Chen TX, Pudasaini B, Guo J, Gong SG, Jiang R, Wang L, Zhao QH, Wu WH, Yuan P, Liu JM. Sex-specific cardiopulmonary exercise testing indices to estimate the severity of inoperable chronic thromboembolic pulmonary hypertension. *Int J Chron Obstruct Pulmon Dis*. 2018;13:385-397.

106. Yuan P, Chen TX, Pudasaini B, Zhang J, Guo J, Zhang SJ, Wang L, Zhao QH, Gong SG, Jiang R, et al. Sex-specific cardiopulmonary exercise testing indices related to hemodynamics in idiopathic pulmonary arterial hypertension. *Ther Adv Respir Dis*. 2017;11:135-145.

107. Swift AJ, Capener D, Hammerton C, Thomas SM, Elliot C, Condliffe R, Wild JM, Kiely DG. Right ventricular sex differences in patients with idiopathic pulmonary arterial hypertension characterised by magnetic resonance imaging: pair-matched case controlled study. *PLoS One*. 2015;10:e0127415.

108. Saouti N, de Man F, Westerhof N, Boonstra A, Twisk J, Postmus PE, Vonk Noordegraaf A. Predictors of mortality in inoperable chronic thromboembolic pulmonary hypertension. *Respir Med*. 2009;103:1013-1019.

109. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, Hodgkins D, Goldsmith K, Hughes RJ, Sheares K, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med*. 2008;177:1122-1127.

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

111. Miyahara S, Schröder TA, Wilkens H, Karliova I, Langer F, Kunihara T, Schäfers HJ. Long-term Outcomes After Pulmonary Endarterectomy in 499 Patients Over a 20-Year Period. *Ann Thorac Surg*. 2021;111:1585-1592.

112. 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;69:116-122.

113. Madani MM. Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: state-of-the-art 2020. *Pulm Circ*. 2021;11:20458940211007372.

114. Hsieh WC, Jansa P, Huang WC, Nižnanský M, Omara M, Lindner J. Residual pulmonary hypertension after pulmonary endarterectomy: A meta-analysis. *J Thorac Cardiovasc Surg*. 2018;156:1275-1287.

115. Delcroix M, Torbicki A, Gopalan D, Sitbon O, Klok FA, Lang I, Jenkins D, Kim NH, Humbert M, Jais X, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2021;57.

116. Mathai SC, Ghofrani HA, Mayer E, Pepke-Zaba J, Nikkho S, Simonneau G. Quality of life in patients with chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2016;48:526-537.

117. 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;160:523-528.

118. Tamada N, Nakayama K, Yanaka K, Onishi H, Shinkura Y, Taniguchi Y, Kinutani H, Tsuboi Y, Izawa KP, Satomi-Kobayashi S, et al. Pulmonary Endarterectomy and Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension- Similar Effects on Health-Related Quality of Life. *Circ Rep*. 2019;1:228-234.

119. Kamenskaya O, Klinkova A, Chernyavskiy A, Lomivorotov VV, Edemskiy A, Shmyrev V. Long-term health-related quality of life after surgery in patients with chronic thromboembolic pulmonary hypertension. *Qual Life Res*. 2020;29:2111-2118.

120. Ohlsson-Nevo E, Hiyoshi A, Noren P, Moller M, Karlsson J. The Swedish RAND-36: psychometric characteristics and reference data from the Mid-Swed Health Survey. *J Patient Rep Outcomes*. 2021;5:66.

121. Ravnestad H, Andersen R, Birkeland S, Svalebjørg M, Lingaas PS, Gude E, Gullestad L, Kvitting JE, Broch K, Andreassen AK. Pulmonary endarterectomy and balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension: Comparison of changes in hemodynamics and functional capacity. *Pulm Circ*. 2023;13:e12199.

122. 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;91:1094-1099.