Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension: a systematic review

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Background: Pulmonary thromboendarterectomy (PTE) is the gold standard treatment for patients with chronic thromboembolic pulmonary hypertension (CTEPH). However, the results are poorly quantified outside a few registry reports and several individual centers.

Methods: A systematic review was performed searching five electronic databases assessing the outcomes for adult patients undergoing PTE for CTEPH. All articles that reported mortality data were included. Primary outcome measures were early/inpatient mortality; secondary outcomes were survival, pulmonary haemodynamics, morbidity and functional status following PTE for CTEPH. Results were pooled via a meta-analysis of proportions and meta-regression.

Results: A total of 5,717 studies were identified, yielding sixty-one relevant papers. Thirty-day mortality ranged from 0.8% to 24.4%, and on meta-analysis was 8.4% [95% confidence interval (CI): 7.2–9.6%]. Mortality was noted to decrease with increasing center volume of PTE cases (P<0.01). Residual pulmonary hypertension was reported in 8.2% to 44.5% of patients.

Conclusions: CTEPH is associated with acceptable short-term mortality and an improvement in pulmonary hemodynamics. With increasing volume of experience and ongoing developments over time peri-operative mortality continues to decrease.

Keywords: Pulmonary endarterectomy; chronic thromboembolic pulmonary hypertension (CTEPH); pulmonary thromboendarterectomy (PTE); pulmonary hypertension

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Introduction

Pulmonary thromboendarterectomy (PTE) represents the treatment of choice for operative patients suffering chronic thromboembolic pulmonary hypertension (CTEPH), and in recent years, guidelines have expanded surgical treatment to all suitable patients (1,2).

In patients who survive acute pulmonary embolism, the literature suggests 0.1% to 4.0% develop CTEPH. This is characterized by thrombus organization within the pulmonary artery and subsequent vascular remodeling in small unobstructed vessels, resulting in pulmonary hypertension and progressive right heart failure (3-5).

The natural history of CTEPH suggests a poor functional quality of life and high mid-term mortality with progressive worsening pulmonary hemodynamics, cardio-pulmonary failure and death. Medically managed CTEPH has a reported three-year mortality rate of 30% to 60% (6,7). Recent series of PTE, however, suggest that this can be improved, and in-patient mortality may be as low as 4% in large volume centers, with survival rates of 90% at three years (8-10).

PTE is being performed and reported by an increasing number of specialist centers worldwide. The procedure has, however, traditionally been associated with high inpatient mortality and morbidity over many years. There is a paucity of robust clinical trial data in the form of randomized control trials. Previous systematic reviews from the 1980s reported a mortality rate of 22%, but by the time of Rahnavardi's 2011 review which examined studies published between 1999 and 2010, mortality rates ranged from 1.3% to 24% (11,12). Since this time, the international literature has greatly expanded. Within the last decade, there have been several changes in international guidelines and peri-operative management; additionally, there has been the development of medical therapies available to patients with CTEPH, along with the advent of balloon pulmonary angioplasty (BPA). We performed the present systematic review to objectively assess the safety and efficacy of PTE for CTEPH based on the complete literature.

Methods

Literature search strategy

A systematic review was performed searching PubMed, Scopus, EmBase, Medline and the Cochrane library using the key search terms "pulmonary hypertension", "hypertension, pulmonary", "chronic thromboembolic pulmonary hypertension" and "endarterectomy", "pulmonary endarterectomy" "pulmonary hypertension/surgery". These were filtered by English language publications reported on adult human subjects. Reference lists of included studies were manually reviewed to screen for further articles.

Any duplicate articles were removed. The titles and abstracts of the remaining articles were reviewed by two independent investigators. To address any inconsistencies, the lists were compared and a third investigator resolved any discrepancies. The PRISMA flow diagram is shown in *Figure 1*.

Inclusion criteria

Studies selected for appraisal could be either prospective or retrospective. Randomized control trials and cohort studies with greater than ten patients were included. Case reports and conference abstracts were excluded. The primary outcome of interest related to inpatient mortality. Preliminary reading identified several studies that excluded patients who died from their reported morbidity and haemodynamic results. Therefore studies were screened such that included articles presented data for entire cohorts, not just surviving candidates who often would have experienced less morbidity and had generally more favourable hemodynamic and comorbid profiles pre-operatively.

Where patient cohorts from frequently publishing centers overlapped, the largest cohort was selected for inclusion.

Studies that presented data within defined subgroups of PTE patients were only included if they presented perioperative mortality and further data for the entire PTE cohort. Three independent reviewers assessed studies for inclusion and extracted data using a proforma. Studies were assessed and data extracted for study size, date of publication, center of publication, operative period, patient numbers, duration of follow-up, inpatient mortality, patient age, gender, 1-, 3-, 5-, 10-, 15- and 20-year survival. Post-operative outcomes of interest included stroke, reoperation for bleeding, post-operative mechanical support and reperfusion pulmonary oedema. Data relating to residual pulmonary hypertension, reoperation and reintervention for pulmonary hypertension were also captured. If studies reported predictive factors for mortality and residual pulmonary hypertension, these were also recorded. Haemodynamic data regarding pre- and post-operative mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), cardiac output (CO), cardiac index (CI), and patients' six-minute walk distance (6MWD), New York Heart Association (NYHA) class or World Health Organization (WHO) functional class were also captured.

Analysis

The pooled mortality was assessed by meta-analysis of proportions or means using a random effects model. The relationship between mortality rate and center volume was analyzed utilizing a DerSimonian-Laird random effects bivariate meta-regression model to account for differing center/surgeon experiences and different operative and management protocols across the included studies. Pooled data are presented with 95% confidence intervals (CI) for outcome data. Analysis was performed in STATA/IC 15.1 (13). A P value <0.05 was considered statistically significant.

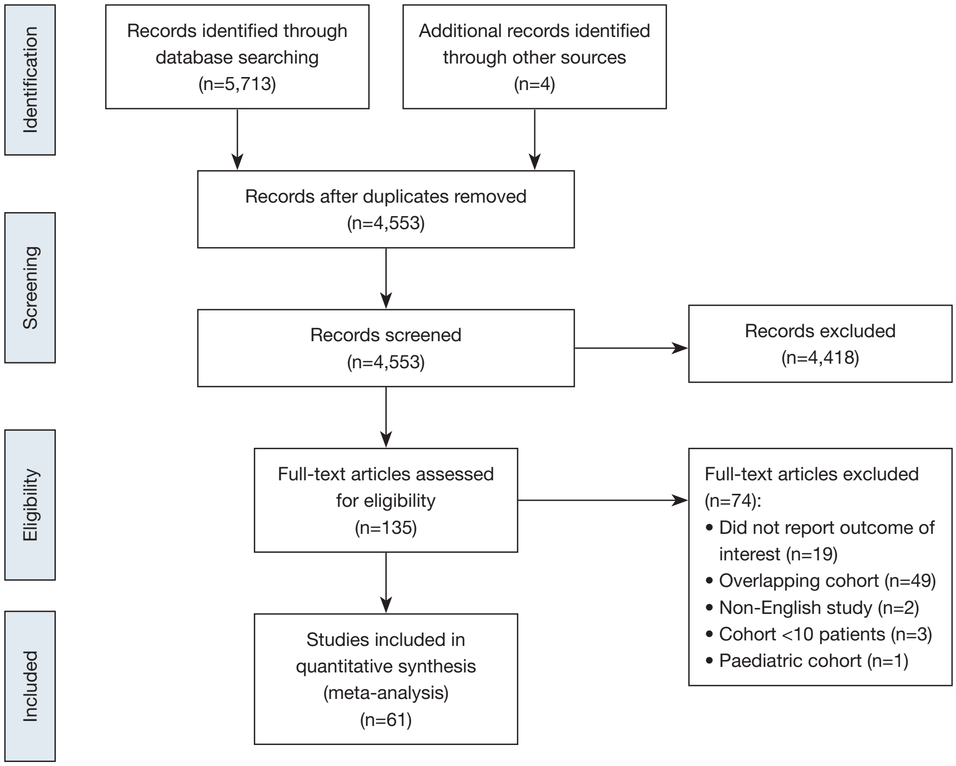

Figure 1 PRISMA diagram.

Publication bias was assessed via an Egger test and funnel plot.

Many morbidity outcomes were heterogeneously/inconsistently reported between studies and were therefore not suitable for meta-analysis; these are reported descriptively.

Study quality was assessed based upon the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool (14). The NHLBI tool assesses whether included studies reported a clear study question with clear objectives, if the cohort was clearly and fully described, if cases were consecutive, if the subjects were comparable, if the intervention was clearly described, if the length of follow-up was adequate, if there was appropriate use of statistical methods and if results were appropriately described.

Results

Literature search

The literature search returned 5,717 publications; 1,164 duplicates were removed. After reviewing the titles and abstracts of these publications, 135 potentially relevant articles were included for full-text review. Following full-text review and removal of overlapping cohorts, sixty-one papers were included for data extraction (*Table 1*). These studies included six national or international databases and fifty-five single-center studies with a cumulative 9,763 patients from individual reporting institutions. Study population sizes ranged from fifteen to 1,500 patients. Papers were published between 1996 and 2021, with operations being performed between 1970 and 2019. Mortality was reported in all series. Eighteen studies reported one-year survival, four reported ten-year survival. Thirty-three reported morbidity outcomes. Thirty-two reported pre- and post-operative haemodynamics.

Quality of evidence

All studies were assessed for quality based on the NHLBI study quality assessment tool, and all scored between six and nine out of nine (*Table 1*). There was one randomized control trial included. Twelve included studies were prospective in nature. Other studies were

Table 1 Studies included

Author (reference)	Year of publication	Country/region	Study period	Study design	Number of patients	Duration of follow-up (years)	Age (years)	Male	Quality assessment	Mortality	Morbidity reported	Haemodynamics reported	Prognostic factors for mortality	Prognostic factors RPH
Delcroix (6)	2016	European Registry	2007–2009	Prospective	404	3.5	60	55.00%	7	5.50%	N	Y	N	N
Madani (8)	2012	USA	1999–2010	Retrospective	1500				8	4.20%	N	N	N	N
Bunclark (9)	2020	UK	2006–2017	Prospective	1324	0.4±0.2	61±21	53.20%	9	3.70%	Y	Y	N	N
Tromeur (10)	2018	France	2005–2009	Retrospective	172	0.6±0.1	60±14	49.00%	9	2.80%	N	Y	Y	Y
Fernandes (15)	2014	USA	2010–2013	Retrospective	476			50.60%	8	0.80%	Y	N	N	N
Mayer (16)	1996	Germany	1989–1995	Retrospective	115	2.3	47	52.30%	7	24.40%	N	Y	N	N
Deng (17)	2021	China (National Registry)	2009–2018	Prospective	81	4.4	45±13	70.40%	9	7.40%	N	Y	Y	N
Miyahara (18)	2021	Germany	1995–2014	Retrospective	499	5.5±4.9	57.5±14.0	54.90%	9	4.20%	N	Y	N	N
Miwa (19)	2018	Japan	1986–2016	Retrospective	159		56.2±11.6	34.60%	9	12.00%	N	Y	Y	N
Amsallem (20)	2018	France	2012–2016	Prospective	486			51.70%	8	4.00%	Y	N	N	N
Hartz (21)	1996	USA	1983–1995	Retrospective	34		49	47.10%	9	9.50%	Y	N	N	N
Nierlich (22)	2016	Austria	1992–2013	Retrospective	214		53.5 (range, 13–84)	55.50%	8	5.70%	Y	Y	Y	N
Coronel (23)	2014	Spain	2000–2012	Retrospective	32		49±16	59.40%	8	18.80%	Y	Y	Y	N
Escribano-Subías (24)	2016	Spain (National Registry)	2006–2013	Prospective	122		50 (IQR 41, 65)	56.00%	9	3.30%	N	Y	Y	Y
Sakurai (25)	2019	Japan	2005–2013	Retrospective	122	6.8	56	28.00%	9	7.40%	Y	Y	Y	N
Korsholm (26)	2017	Denmark	1994–2016	Retrospective	239	4.4	60±12.8	55.00%	9	8.40%	Y	Y	N	N

Table 1 (*continued*)

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Author (reference)	Year of publication	Country/region	Study period	Study design	Number of patients	Duration of follow-up (years)	Age (years)	Male	Quality assessment	Mortality	Morbidity reported	Haemodynamics reported	Prognostic factors for mortality	Prognostic factors RPH
Kallonen (27)	2020	Sweden	1997–2018	Retrospective	100	7.2	62±13	61.00%	9	7.00%	N	Y	N	N
Gan (28)	2010	China	1989–2008	Retrospective	360	7.9±4.5	44.3±13.4	64.40%	9	4.40%	Y	Y	N	N
Rubens (29)	2007	Canada	1995–2006	Retrospective	180		50.7 ± 14.9	51.00%	9	7.80%	Y	Y	N	N
Miller (30)	1998	USA	1985–1995	Retrospective	25		46	84.00%	9	8.10%	N	Y	Y	N
López Gude (31)	2017	Spain	1996–2016	Retrospective	160	2.9		54.40%	9	5.60%	Y	N	N	N
Fragata (32)	2020	Portugal	2008–2019	Retrospective	19		54.8±14.8	36.80%	8	10.50%	Y	Y	N	N
Vanden Eynden (33)	2016	Belgium	2007–2012	Retrospective	30	1	57.5±13.7	50.00%	8	10.00%	Y	Y	N	N
Oh (34)	2013	Korea	1999–2011	NR	16	4.5	44±14	62.50%	8	10.80%	N	Y	N	N
Kelava (35)	2019	USA	1997–2015	Retrospective	150				7	6.90%	Y	N	N	N
Cain (36)	2021	USA	1993–2015	Retrospective	159	14.7	55.3 (IQR 42.2–66.1)	46.50%	9	23.50%	Y	Y	Y	N
Leung Wai Sang (37)	2016	Canada	2004–2012	Retrospective	38		54.2±12.1	44.70%	8	7.90%	Y	Y	N	N
Hobohm (38)	2021	Germany (National Registry)	2006–2016	Retrospective	1398		62	43.20%	9	2.50%	Y	Y	Y	N
Lankeit (39)	2018	Germany	2014–2015	Prospective	237	1.3	62 (range, 52–72)	54.00%	9	13.00%	N	Y	Y	N
Martinez Santos (40)	2021	Spain (National Registry)	2007–2018	Retrospective	350		53±14	56.30%	8	3.80%	N	Y	Y	N
Yanaka (41)	2018	Japan	2001–2017	Retrospective	44	1.5±0.3		36.40%	9	11.40%	N	N	Y	N
Gu (42)	2010	China	2002–2006	Retrospective	15	3.9±1.5	41.5±14.6	80.00%	9	13.30%	Y	Y	N	N

Table 1 (*continued*)

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Author (reference)	Year of publication	Country/region	Study period	Study design	Number of patients	Duration of follow-up (years)	Age (years)	Male	Quality assessment	Mortality	Morbidity reported	Haemodynamics reported	Prognostic factors for mortality	Prognostic factors RPH
Freed (43)	2008	UK	1997–2006	Retrospective	229		55.2	54.30%	9	21.30%	N	Y	N	N
Matsuda (44)	2006	Japan	1995–2005	Retrospective	102	3.1±2.6	51.9±13.0	38.20%	9	7.80%	Y	Y	N	N
van der Plas (45)	2011	Netherlands	2003–2009	Retrospective	96	1.5	54±14	40.80%	9	10.40%	N	Y	N	Y
Hosokawa (46)	2011	Japan	2003–2007	Retrospective	51		52.2±12.2	41.20%	7	3.90%	N	Y	N	Y
Kamenskaya (47)	2020	Russia	2011–2016	Prospective	128	3	49.1±12.9	67.20%	9	6.30%	Y	N	Y	N
Ghio (48)	2021	Italy	1994–2017	Prospective	782	4.7	60±15	47.00%	9	9.40%	Y	Y	N	N
Sihag (49)	2017	USA	1998–2016	Retrospective	134		54±15	60.00%	8	3.70%	N	Y	N	N
Narayana Iyengar (50)	2010	India	2008–2009	Retrospective	41	0.5	41.33	73.20%	8	12.20%	Y	Y	N	N
Mikus (51)	2008	Italy	2004–2007	Retrospective	40	0.6	61.6	30.00%	8	5.00%	Y	Y	N	N
Archibald (52)	1999	USA	1970–1994	Prospective	308	3.3±2.7	56.2±15.6	58.80%	7	9.50%	N	N	N	N
Chen (53)	2019	Taiwan	2001–2017	Prospective	19	3.1±3.6		21.10%	8	11.00%	Y	Y	N	N
Ji (54)	2006	China	1997–2005	NR	30	3.1	45.7	80.00%	8	3.30%	N	Y	N	N
Yan (55)	2019	China	2015–2017	Retrospective	58	1.8	48.2±11.6	63.80%	9	1.70%	Y	Y	N	N
Hagl (56)	2003	Germany	2000–2002	Retrospective	30	1.3	58±13	53.30%	9	10.00%	Y	Y	N	N
Macchiarini (57)	2006	Germany, Spain	2004–2005	Prospective RCT	30	1.5	55±12	63.30%	8	3.30%	Y	Y	N	N
Türer Cabbar (58)	2021	Turkey	2016–2017	Prospective	64	2.9±2.7	53.45±15.31	66.30%	9	6.30%	N	Y	Y	N
Yanartas (59)	2015	Turkey	2011–2013	Retrospective	106			39.60%	9	20.80%	N	N	Y	N

Table 1 (*continued*)

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Author (reference)	Year of publication	Country/region	Study period	Study design	Number of patients	Duration of follow-up (years)	Age (years)	Male	Quality assessment	Mortality	Morbidity reported	Haemodynamics reported	Prognostic factors for mortality	Prognostic factors RPH
Puis (60)	2005	Belgium	1999–2003	Retrospective	40	1.8	57±18	35.00%	8	7.50%	Y	Y	N	N
Dartevelle (61)	1999	France	1996–1998	Retrospective	68		54.3±13.5	51.50%	8	13.20%	Y	Y	N	N
Gilbert (62)	1998	USA	1994–1997	Retrospective	17				7	23.50%	N	N	Y	N
Raza (63)	2018	USA	2013–2016	Retrospective	71		56±16	46.00%	8	24.00%	Y	N	N	N
Kim (64)	2017	Korea	1994–2015	Retrospective	37	11.8	52.6±12.6	62.20%	9	8.40%	N	Y	Y	N
Schölzel (65)	2011	Netherlands	2000–2009	Retrospective	74	3.7±2.2	55.9±13.8	49.00%	9	12.50%	Y	N	N	N
Segel (66)	2019	Israel	2008–2017	Retrospective	28		46 (range, 19–80)	50.00%	6	6.80%	N	Y	N	Y
Balki (67)	2021	Canada	2014–2017	Retrospective	127	1	58±14	42.00%	8	7.10%	N	Y	N	N
Cruz-Suarez (68)	2018	Colombia	2009–2017	Retrospective	21		48 (range, 30–70)	42.90%	7	1.60%	N	Y	N	N
Dyk (69)	2007	Poland	1995–2008	NR	96		51	66.70%	7	6.50%	Y	Y	Y	N
Siennicka (70)	2019	Poland	2015–2018	NR	31	1.8	50.9±14.7	45.00%	7	7.30%	N	Y	N	N
Mayer (71)	2011	Multi-national Registry	2007–2009	Prospective	386	1	60	54.10%	9	4.70%	Y	Y	Y	Y

NR, not reported; RCT, randomized control trial; IQR, interquartile range; Mortality (in-patient/30 day); Y, yes; N, no; RPH, residual pulmonary hypertension.

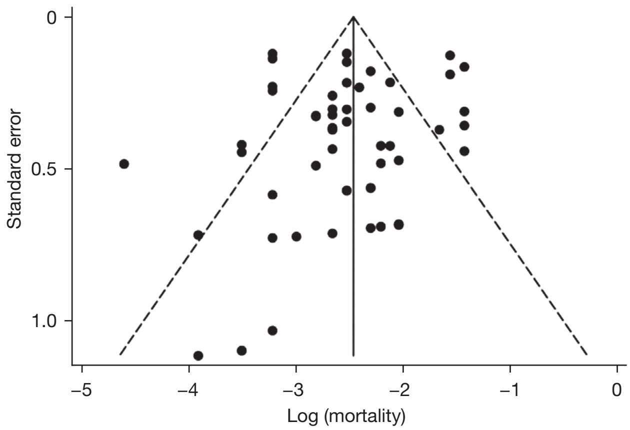

Figure 2 Funnel plot of studies. Assessment of bias, Egger test (P=0.53).

either retrospective or not specified. Very few papers explicitly cited selection criteria for acceptance or exclusion from PTE in CTEPH. Two included studies were from multinational registries. Four included studies were from national registries. These studies are likely to overlap with several of the single center studies.

Search results were assessed for publication bias using the Egger test, which suggested minimal publication bias (P=0.53) (*Figure 2*).

Mortality

Inpatient mortality ranged from 0.8% to 24.4% across the sixty-one studies as shown in *Table 1*. Overall mortality via the meta-analysis of proportions was 8.4% (95% CI: 7.2–9.6%). I^2=81.1% suggesting considerable heterogeneity of included studies. Mortality by center was inversely associated with the reported volume of cases (P<0.01).

Twenty studies reported factors linked to mortality (*Table 1*). The most frequently noted were extremely raised PVR pre-operatively, although cut-offs varied between 800–1,100 Dynes (10,16,21,22). Patients with extremely raised PVR, however, had the greatest overall decrease in PVR post-operatively (22). Additionally, poorer functional status, assessed by either 6MWD or NYHA class was associated with increased peri-operative mortality (16,22).

Mid-to-long-term survival

One-year survival was reported in eighteen of the included studies and ranged from 72% to 95.1%, with a median of 91.2% (Table S1). At three years, survival ranged from 67% to 92.5%. Within the European and Chinese registries, three-year survival was 89% (6,17). At five years, survival was 50% to 89.2% as reported across fourteen studies; nine of these studies reported survival of >80% (6,8,10,17,19,22-27, 29,35,40,43,44,53,64,66). Previous systematic reviews only included two studies reporting 10- to 15-year survival (12,28,43). The current systematic review included nine studies reporting ten-year survival, which ranged from 62% to 86.1% with a median of 75% (8,19,22,25-28,43,64). Four studies reported 15-year survival: three reported rates between 55% to 59% and Gan *et al.* reported fifteen-year survival of 29.6% in those with residual pulmonary hypertension compared to 91% in those without residual hypertension (18,27,28,64). No studies reported twenty-year survival.

Major morbidity

Major morbidity was inconsistently reported between studies and is outlined in Table S2. The analysis included twenty-two studies, and the most frequent complication was reperfusion pulmonary oedema. Rates of reperfusion oedema ranged from 3% to 96%, with a median of 18.8% (15,23,26,28,31-33,36-38,42,44,48,50,53,55-57, 61,63,65,71).

Mechanical support [generally extracorporeal membrane oxygenation (ECMO), but in one series including intra-aortic balloon pump] was reported in twenty-two of the included studies. It was required in 0% to 56.3% of patients (median 5.5%), with indications including right ventricular support, failure to wean from cardiopulmonary bypass and failure to oxygenate due to reperfusion pulmonary oedema (9,32-34). In the two largest reporting series it was required in 5.1 and 5.5% of patients (9,38). Survival for patients requiring ECMO ranged from 25% to 57% (25,35,72).

Bleeding was heterogeneously reported with multiple definitions, including a return to theatre for bleeding, various decreases in haemoglobin or transfusion of greater than two units of packed red blood cells. Rates of reported bleeding ranged from 0% to 25% (23,26,29,31,32,36-38, 42,48,51,65).

Neurological complications were inconsistently reported, with many studies reporting prolonged sedation or confusion as neurological complications. Proven stroke with residual neurological deficit was generally low (21,26,31,44,48).

Duration of hospitalization

Length of intensive care unit stay was reported in twenty-one studies and ranged from four to 15.6 days. This is greatly dependent on the hospitals' bed flow and ward capacity/ceilings of care. Total post-operative hospital length of stay ranged from ten to forty-five days, with a median of fifteen days (Table S2) (9,15,22,23,25,32,33,36-39,42,44,48-50,53,55-57,62,65,68,69).

Haemodynamics

Thirty-two studies reported pre- and post-operative haemodynamics (Table S3). All thirty-two noted marked improvement in right heart and pulmonary vascular hemodynamics. Postoperatively, CO and CI also improved significantly. In the largest series, PVR improved from 668.8±474.4 to 254.4±224 Dynes across the cohort, with mPAP improving from 45±15 to 25±13 mmHg (9).

Residual pulmonary hypertension was reported in fifteen of the included studies, rates of which ranged from 8.2% to 44.5% (9,23,24,26,30,31,40,44,45,46,49,55,64,66,71). However, it is worth noting that not all studies used the same definition for residual pulmonary hypertension and that many did not explicitly state a defined threshold for residual pulmonary hypertension. Additionally, during recent years, the definition of pulmonary hypertension as per European guidelines has decreased from an mPAP of 25 to 20 mmHg. Many earlier studies also used 30 mmHg as a threshold for residual pulmonary hypertension or only considered it significant if additional medical therapy was initiated (2,73).

Six studies reported factors associated with residual pulmonary hypertension. Raised pre-operative PVR and distal disease were associated with residual pulmonary hypertension (10,24,45,46,66,71).

Recently, BPA has emerged as an adjunct treatment for patients with residual pulmonary hypertension. Several studies reported on rates of BPA after PTE. These ranged from 2.0% to 22.7% for residual pulmonary hypertension or planned hybrid procedures for surgically inaccessible lesions (19,25,40,41).

Functional status

Functional status was noted to improve in all studies reporting either NYHA, WHO functional status and 6MWD (see Table S3). Pre-operatively, 66.4–100% of patients were reported as being WHO/NYHA class III or IV, but only 0% to 25% remained in these functional classes after PTE (Table S3). There was also a corresponding improvement in 6MWD following PTE. All studies noted an improvement in 6MWD, with the greatest increase being more than 200 m (42). Several studies noted major improvements continuing up to the six to twenty-four month mark post-PTE (43-45,74).

Discussion

The present systematic review incorporates the sixty-one most complete studies from hospitals publishing the outcomes of PTE for CTEPH. Although still a relatively morbid procedure by modern surgical standards, this systematic review suggests that overall mortality in a meta-analysis of proportion was was 8.4% (95% CI: 7.2–9.6%). Furthermore, in experienced centers, this may be less than 5% and five-year survival may be as high as 89.2%. In comparison, the three-year mortality rate for medically managed CTEPH is 30% to 60% (6,7).

In contrast to previous reviews, this systematic review has shown a clear association between center volume and mortality. This corroborates the suggestions of the European Database linking PTE outcomes to unit volume, as units performing less than ten surgeries per year had an average inpatient mortality of 8.8%, whereas those performing eleven to fifty-50 surgeries per year reported a mortality rate of 4.5% and centers performing >50 surgeries per year had a mortality rate of 3.4% (6). Several studies reported decreasing mortality over time as the reporting center's experience expanded (18-20,75). Even very experienced national referral centers report decreasing mortality in recent cohorts. Amsallem *et al.* at France's Marie Lannelongue Hospital reported a thirty-day mortality of 1.9% in their most recent cohort in 2016, compared to 4.0% overall from 2012 to 2016 (20). Similarly, Bonderman *et al.*, reporting the outcomes from the Viennese center, noted a gradual decline in mortality from 27% [1992–1995], to 15% [1996–1999], to 6% [2000–2004], to 5% [2004–2006] (75).

Reporting the results of the Spanish national referral center López Gude *et al.* noted a distinct learning curve (31). Mortality overall was 5.6% but once the learning curve was overcome, this dropped to 2.6%. The learning curve was felt to encompass the first forty-six cases. However, in a study of almost 500 patients, Miyahara *et al.* noted decreasing mortality with each 100-patient block (18). It is important to recognize that this learning curve likely not only affects surgeons taking on a new, challenging procedure but the whole multidisciplinary team including anaesthetic, perfusion, intensive care and ward staff as they adapt to looking after patients with a complex interplay of respiratory and right heart pathophysiology.

In addition to centers overcoming the surgical learning curve, there have been ongoing general improvements such as the advent of BPA, and development of medications such as Bosentan and Riociguat mid-way through the 2000s and 2010s (76,77). Over time there has been a clear trend both within individual centers and the overall literature to decreasing mortality; this suggests that these developments along with ongoing refinements in intensive care and surgical technique continue to improve outcomes.

Independent predictors of mortality included increasing pre-operative PVR, age and poorer functional status. Ten-year survival of patients with residual pulmonary hypertension was 67.9%±4.7% compared to 89.0%±2.7% in those without (18). Hosokawa and Gan *et al.* also noted worsened survival at ten and fifteen years depending if the thrombus location was proximal or distal (28,46). Proximal disease was associated with a 94.6% survival rate, compared to 71.8% for distal disease. At fifteen-years post-PTE, this difference became even more marked as survival for proximal disease was 91% against 29.6% for patients with distal disease (28).

Residual pulmonary hypertension is associated with not only worsening survival but also worsened quality of life. Kamenskaya *et al.* defined residual pulmonary hypertension as the factor that most affects quality of life after PTE (47). Additionally, those with residual pulmonary hypertension also had a greater incidence of hospitalization, persistent low functional capacity and death (48).

A previous meta-analysis reported that 25% of patients suffered residual pulmonary hypertension (78). However, whilst a worthy endeavour to attempt to quantify this problem, residual pulmonary hypertension is difficult to accurately analyze and quantify. This relates to heterogenous definitions for residual pulmonary hypertension. In recent years the definition has changed within international guidelines, and furthermore there is significant variation in the threshold used between papers, ranging from mPAP 20–30 mmHg or using the initiation of medical therapy as indicative of residual/recurrent pulmonary hypertension. These heterogenous definitions make combining these reported rates unreliable. This systematic review notes that 8.2% to 44.5% (median 20%) of patients had residual pulmonary hypertension (47-49).

Patients with the highest pre-operative PVR were more likely to have residual pulmonary hypertension and had higher rates of peri-operative mortality. However, in several of the largest volume referral centers, including the University of California, San Diego and Royal Papworth, patients were not deemed ineligible for PTE based on the severity of pulmonary hypertension or age alone (1,8,9,15). It has also been suggested that the classification of patients as operable or inoperable is even less relevant in the era of BPA, as patients may benefit from a ‘hybrid’ approach of both PTE and BPA in the course of their disease process in addition to medical therapy (1).

Morbidity was inconsistently described. Although utilization of ECMO and reperfusion oedema were well described over a number of studies, most complications were poorly defined and reported. Renal failure rates were as high as 9.4% but were only reported in a handful of series (23,39). Mediastinitis and deep sternal wound infection rates, associated with deep hypothermic arrest in other forms of cardiac surgery, were reported in up to 6% of patients in international registries, but were not reported in series from individual centers (16). Whilst it is a positive step that three significant national registries published results in 2021, only one of these published morbidity data and pre-and post-operative haemodynamic outcomes (17,38,40). It will become increasingly important that these large-volume, well-supported prospective registries continue to collect and report data for CTEPH and patients undergoing PTE. Currently, there is a dearth of randomized controlled trials pertaining to PTE management. Moving forward, it is important that the existing prospective registries adopt similar definitions for blood loss/blood conservation, renal failure and other major complications so that CTEPH morbidity can be better quantified, reported and optimized.

Limitations

There are a number of important limitations when interpreting the results described in the present study. There was significant heterogeneity for some of the reported outcomes. In particular, these were bleeding, neurological complications, reperfusion pulmonary oedema and residual pulmonary hypertension given the changing definitions. Studies also inconsistently reported loss to follow-up, and some studies reported outcomes with high complication rates in small patient populations. The observational nature of the majority of included studies also presents an inherent source of bias in the present study. Additionally, different reporting centers will have different surgeon experiences, patient populations and selection, and variance in surgical technique.

Conclusions

This systematic review reports the outcomes for studies from international PTE centers in the treatment of CTEPH. These outcomes suggest that PTE for CTEPH can be performed with low morbidity and mortality rates, and whilst these continue to improve over time, outcomes remain linked to center volume. Patients can achieve markedly improved haemodynamic indices, and this is associated with improved mid- and longer-term survival. PTE remains the gold standard treatment for surgically accessible CTEPH.

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Footnote

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Supplementary

Table S1 Mortality (in-patient/30 day) and survival

Author (Reference)	Mortality	1-year survival	3-year survival	5-year survival	10-year survival	15-year survival	Prognostic factors for Mortality
Mayer (16)	24.4%						N
Hartz (21)	9.5%						N
Gilbert (62)	23.5%						Y
Miller (30)	8.1%						Y
Archibald (52)	9.5%	81.5%					N
Dartevelle (61)	13.2%						N
Hagl (56)	10.0%						N
Puis (60)	7.5%	87.5%					N
Ji (54)	3.3%						N
Macchiarini (57)	3.3%						N
Matsuda (44)	7.8%	90.6%	89.8%				N
Rubens (29)	7.8%	90.9%	84.0%				N
Dyk (69)	6.5%	91.2%					Y
Mikus (51)	5.0%						N
Freed (43)	21.3%		74.6%	72.3%	69.3%		N
Narayana Iyengar (50)	12.2%						N
Gan (28)	4.4%				71.8/94.6%	29.6/91.0%	N
Gu (42)	13.3%						N
van der Plas (45)	10.4%						N
Hosokawa (46)	3.9%						N
Schölzel (65)	12.5%						N
Mayer (71)	4.7%	93.0%					Y
Madani (8)	4.2%			82.0%	75.0%		N
Oh (34)	10.8%						N
Fernandes (15)	0.8%						N
Coronel (23)	18.8%	72.0%	67.0%	67.0%			Y
Yanartas (59)	20.8%						Y
Vanden Eynden (33)	10.0%						N
Leung Wai Sang (37)	7.9%						N
Nierlich (22)	5.7%	91.0%		79.6%	66.5%	56.2%	Y
Escribano-Subías (24)	3.3%	95.1%		86.3%			Y
Delcroix (6)	5.5%	93.0%	89.0%				N
Korsholm (26)	8.4%		84.0%	77.0%	62.0%		N
López Gude (31)	5.6%						N
Sihag (49)	3.7%						N

Table S1 (*continued*)

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Table S1 (*continued*)

Author (Reference)	Mortality	1-year survival	3-year survival	5-year survival	10-year survival	15-year survival	Prognostic factors for Mortality
Kim (64)	8.4%			84.8±1.9%	77.1±2.7%	59.2±5.3%	Y
Miwa (19)	12.0%	88.1%	86.6%	84.1%	80.6%		Y
Yanaka (41)	11.4%						Y
Amsallem (20)	4.0%						N
Tromeur (10)	2.8%	93.1%	92.5%				Y
Raza (63)	24.0%						N
Cruz-Suarez (68)	1.6%						N
Lankeit (39)	13.0%						Y
Chen (53)	11.0%	89.0%	81.0%	50.0%			N
Kelava (35)	6.9%	87.2%					N
Sakurai (25)	7.4%	91.8%	89.2%	89.2%	86.1%		Y
Yan (55)	1.7%						N
Segel (66)	6.8%	93.0%	91.0%	89.0%			N
Siennicka (70)	7.3%						N
Bunclark (9)	3.7%						N
Kallonen (27)	7.0%			80.0%	69.0%	55.0%	N
Fragata (32)	10.5%						N
Kamenskaya (47)	6.3%						Y
Cain (36)	23.5%						Y
Türer Cabbar (58)	6.3%						Y
Ghio (48)	9.4%						N
Miyahara (18)	4.2%						N
Balki (67)	7.1%						N
Hobohm (38)	2.5%						Y
Martinez Santos (40)	3.8%	94.6%	89.7%	82.5%			Y
Deng (17)	7.4%	92.6%	89.6%	87.5%			Y

Y, yes, discuss prognostic factors for mortality; N, no discussion of prognostic factors for mortality.

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Table S2 Morbidity

Author (Reference)	Stroke/ Neurology	Major Bleeding	Post-operative Mechanical Support	Reperfusion Oedema	ICU LoS (Days)	Hospital LoS (Days)
Mayer (16)						
Hartz (21)	4.8%		4.8%		7.5 (IQR 1.1–22)	
Gilbert (62)						
Miller (30)						
Archibald (52)						
Dartevelle (61)				33.8%		
Hagl (56)				23.3%	5±9	
Puis (60)			7.5%			
Ji (54)						
Macchiarini (57)				0.0%	6.6±8.5	
Matsuda (44)	4.7%			9.0%	4.1±2.4	19.5±10.5
Rubens (29)		4.9%	8.8%			
Dyk (69)			14.4%		5 (0–56)	
Mikus (51)		5.0%	5.0%			
Freed (43)						
Narayana Iyengar (50)			2.4%	19.3%	11.25	
Gan (28)				9.4%		
Gu (42)		6.7%		20.0%	6.1±4.3	
van der Plas (45)						
Hosokawa (46)						
Schölzel (65)		25.0%	56.3%	31.3%	15.6±16.4	29.1±22.2
Mayer (71)	11.2%		3.1%	9.6%		
Madani (8)						
Oh (34)						
Fernandes (15)				23.1%	4	11
Coronel (23)		16.1%		25.8%	8	17
Yanartas (59)						
Vanden Eynden (33)			0.0%	3.3%	8.1±14.4	30.5±12.1
Leung Wai Sang (37)		13.2%		44.7%	5.5	15
Nierlich (22)			2.0%		4.8 (IQR 2.4–7.9)	10.0 (IQR 7.0–17.0)
Escribano-Subías (24)						
Delcroix (6)						
Korsholm (26)	1.7%	9.2%	3.8%	13.5%		
López Gude (31)	TIA 3.8%	5.0%	5.0%	18.8%		
Sihag (49)					4.6±4.7	12.6±9.0

Table S2 (*continued*)

https://dx.doi.org/10.21037/acs-2021-pte-25

Table S2 *(continued)*

Author (Reference)	Stroke/ Neurology	Major Bleeding	Post-operative Mechanical Support	Reperfusion Oedema	ICU LoS (Days)	Hospital LoS (Days)
Kim (64)						
Miwa (19)						
Yanaka (41)						
Amsallem (20)			9.1%			
Tromeur (10)						
Raza (63)				96.0%		
Cruz-Suarez (68)					4 [IQR 3–7]	12 (9–19)
Lankeit (39)						
Chen (53)	15.8%		21.1%	68.4%	8±13	19±26
Kelava (35)			9.3%			
Sakurai (25)			25.4% ECMO, 9.0% IABP		7	45
Yan (55)	0.0%		3.4%	6.9%	6 (IQR 5–7)	
Segel (66)						
Siennicka (70)						
Bunclark (9)			5.5%		4±3	14.5±10
Kallonen (27)						
Fragata (32)		0.0%	0.0%	5.0%	9.2±8.5	21.5±12.9
Kamenskaya (47)	0.6%					15
Cain (36)	2.9%	8.8%	17.6%	29.4%		10.8
Türer Cabbar (58)						
Ghio (48)	1.0%	18.0%	14.0%	3.0%	10.9±13.6	19.0±15.0
Miyahara (18)						
Balki (67)						
Hobohm (38)	1.3%	11.4%	5.1%	9.7%		15 (IQR 13–18)
Martinez Santos (40)						
Deng (17)						

ICU, Intensive Care Unit, LoS, Length of Stay, TIA, Transient Ischaemic Attack, ECMO, Extracorporeal Membrane Oxygenation, IABP, Intra-Aortic Balloon Pump, IQR, Inter-quartile Range.

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Table S3 Haemodynamic and Functional outcomes

Author (Reference)	Mean Pulmonary Artery Pressure, mmHg		Pulmonary Vascular Resistance, Dynes		Cardiac Output, L/min		Cardiac Index, L/min/m^2		NYHA/WHO Class III–IV		6 Minute Walk Distance		RPH	Subsequent BPA	Prognostic factors RPH
	Pre-Op	Post-op	Pre-Op	Post-op	Pre-Op	Post-op	Pre-Op	Post-op	Pre-Op	Post-op	Pre-op	Post-op			
Mayer (16)	49±19	23±10	1015±454	198±72			2.0±0.7	2.9±0.5	95.4%	4.6%					N
Hartz (21)									76.2%						N
Gilbert (62)															N
Miller (30)	45.3±10.8	23.6±8.42		243 (IQR 174–338)		5.0±1.21	2.1±0.6	2.8±0.58	84.0%	5.5%		391±111	44.5%		N
Archibald (52)										7.8%					N
Dartevelle (61)	54±13	30.2±11.8	1207±416	519±250	3.8±0.81	5.0±1.3	2.1±0.51	2.8±0.6	97.1%	4.4%					N
Hagl (56)	56±17	26±10	873±248	290±117	4.2±0.8	5.9±1.4	1.8±0.3	2.8±0.4	100.0%	0.0%					N
Puis (60)	50±11	38±10	1246±482	515±294			1.54±0.54	2.63±0.75							N
Ji (54)							1.64 ± 0.47	2.58 ± 0.51	100.0%	4.0%					N
Macchiarini (57)	57±18	25±7	1110±192	279±98			1.7±0.3	2.9±0.4	100.0%	0.0%					N
Matsuda (44)	47.3±10.4	27.5±7.7	780±258	368±120				2.9±0.8					20.0%		N
Rubens (29)	46±9	46±9	1072±448	346±256			2.0±0.6	2.5±0.6			358±102	490±80			N
Dyk (69)	51±13.1	3.7±11.1	860±386.36	337.6±200.6			2.3±0.5	2.75±0.8	86.9%						N
Mikus (51)	48±10		793.5±284	286±143			2.3±0.4		75.0%	0.0%	371.1±108.9	483±114.1			N
Freed (43)	47±14	25±14	800±494	244±253			1.9±0.7	2.5±0.6	87.6%	9.0%	269±123	392±108			N
Narayana Iyengar (50)	40.98±9.29	41.3±7.36	418±95.88	142.45±36.3			1.99±0.20	3.28±0.56	61.0%						N
Gan (28)	81.48±17.2		1512						99.9%						N
Gu (42)	49.3±18.6	26.8±10.5	938.8±464.1	316.8±153.3			2.31±0.69	3.8±1.2	100.0%	0.0%	308±96	527±132			N
van der Plas (45)	43.7±10.9	24.7±7.2	806±387	422±146	5.0±1.3				80.3%	0.0%	440±109	524±83	31.3%		Y
Hosokawa (46)	46.6±10.1	25.1±13.7	1142±454	496±363	3.16±0.99	3.75±0.93					375±102	429±111	39.2%		Y
Schölzel (65)									68.8%						N
Mayer (71)	48		736	248			2.2				362	459	16.7%		Y
Madani (8)															N
Oh (34)	43.5±9.7		602.2±39.0		4.3±1.4		2.6±1.0		62.2%		380.0 (IQR 300.0–491.0)				N
Fernandes (15)									86.1%						N
Coronel (23)	52±13	26±9	1020±537	296±171			1.94±0.56	2.49±0.43	72.0%	0.0%	397±114	473±111	33.0%		N
Yanartas (59)									71.7%						N
Vanden Eynden (33)	46.5±11.6	27.5±17.4	847.5±432.0	358.7±264.9	3.77±0.97	4.3±2.1	2.0±0.51	2.31±1.11	89.7%						N
Leung Wai Sang (37)	49.9±14.2	32.0±7.3	1209.1±722.9				2.1±0.7	3.1±1.0	97.4%	87.5%					N
Nierlich (22)	47 (IQR 42.0–44.0)		600 (IQR 560–1120)		2.6 (IQR 2.2–3.0)				78.1%						N
Escribano-Subías (24)	48.0±12.6		688 (476,1048)		4.2				72.1%		400 (IQR 290, 475)		41.2%		Y
Delcroix (6)	48		728				2,2		81.0%		340				N
Korsholm (26)	48.4±10.7	33.4±8.9	857±398	289			2.1±0.6	3±0.7	92.5%	16.0%	348	448±104	17.5%		N
López Gude (31)									81.9%	6.3%			19.6%		N
Sihag (49)	49	22.7±7	639±373		4.7±1.5				66.4%				8.2%		N

Table S3 (*continued*)

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Table S3 (*continued*)

Author (Reference)	Mean Pulmonary Artery Pressure, mmHg		Pulmonary Vascular Resistance, Dynes		Cardiac Output, L/min		Cardiac Index, L/min/m^2		NYHA/WHO Class III–IV		6 Minute Walk Distance		RPH	Subsequent BPA	Prognostic factors RPH
	Pre-Op	Post-op	Pre-Op	Post-op	Pre-Op	Post-op	Pre-Op	Post-op	Pre-Op	Post-op	Pre-op	Post-op			
Kim (64)	44.8±12.2	23.5±7.1	813.7±454.9	259.7±158				4.9±122.0	89.8%		346.1±127.3		33.3%		N
Miwa (19)	46.4±10.0		824				2.6±0.7		74.5%		367.2±89.6			8.2%	N
Yanaka (41)									77.3%	13.6%				22.7%	N
Amsallem (20)									74.5%						N
Tromeur (10)	48±11	28±10	773±353	307±221	4.53±1.35	5.50±1.41			83.0%	25.0%	310±159	399±146			Y
Raza (63)															N
Cruz-Suarez (68)	45±13		856 [587-1217]								361±165	463±157			N
Lankeit (39)	48.1 ± 9.5		762 ± 328		4.4±1.3		2.2±0.5		84.0%	16.0%	310±128				N
Chen (53)	51±11		1048		3.0±1.0		1.9±0.6		100.0%	12.0%	326±62	420±63			N
Kelava (35)															N
Sakurai (25)	47	20	832	219			2.28	2.7	96.0%	12.3%				15.6%	N
Yan (55)	49±13	22	724 (IQR 538-1108)	206 (IQR 141-284)					60.3%	98.1%			12.1%		N
Segel (66)	41.3/-11.9	25.2±11.2	521±264		4.7±1.2				74.0%		389±130	480±141	18.8%		Y
Siennicka (70)	47	25	579	163	3.6	6.1	1.9	3.2							N
Bunclark (9)	45±15	25±13	668.8±474.4	254.4±224			2.17±0.76	2.3±0.68	86.3%		309±170	366±159	35.0%		N
Kallonen (27)	45±11								95.0%						N
Fragata (32)	45.6±13.4		1821.6±575.1				2.02±0.68		94.7%						N
Kamenskaya (47)									18.1%						N
Cain (36)	53.5±2.5		1,093.9±116												N
Türer Cabbar (58)	42.05±15.77		620.83±373.91		4.44±1.23		2.36±0.63								N
Ghio (48)	47±12	28±10	810±443	215±139			2.0±0.7	3.2 ± 0.7							N
Miyahara (18)	45±11	24±8					2.1±0.5	2.8±0.5							N
Balki (67)	48		1240 (160-4760)				2.2 (1.0-4.5)		67.9%	10.7%	338 (IQR 300-377)	437 (IQR 390-513)			N
Hobohm (38)	43 (IQR 34-50)	29 (IQR 26-33)	576 (IQR 400-824)	Median 384	4.5 (IQR 3.6-5.5)		2.3 (IQR 1.9-2.7)		78.5%						N
Martinez Santos (40)	44±10		752±440				2.3±0.5		68.3%		380±119		16.8%	2.0%	N
Deng (17)	52±10		1136±441				2.3±1.0		59.0%		367±102				N

NYHA, New York Heart Association, WHO, World Health Organization, RPH, Residual Pulmonary Hypertension, BPA, Balloon Pulmonary Angioplasty, IQR, Inter-Quartile Range.

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