



Long-term Outcomes and Predictors of Chronic Thromboembolic Pulmonary Hypertension After Pulmonary Endarterectomy

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Abstract

Background: Pulmonary endarterectomy (PEA) is the preferred treatment for CTEPH patients which can significantly improve symptoms and pulmonary hemodynamics. Therefore, this retrospective study evaluated the long-term outcomes after pulmonary endarterectomy (PEA) and analyze the predictors of long-term outcomes for chronic thromboembolic pulmonary hypertension (CTEPH).

Methods: From 2002–2020, 76 CTEPH patients successfully discharged after PEA in Beijing Chaoyang Hospital were followed-up by scheduled clinical visits or telephone interviews. The follow-up time lasted for 18 years and median time was 7.29 years.

Results: The survival rate at 1,3,5,10,15 years postoperatively was 100.00%, 97.10%, 95.40%, 89.80% and 82.90%, respectively. Multivariate logistics regression analysis showed that postoperative mPAP (hazard ratio: 1.144; 95%confidence interval: 1.018–1.285; $P=0.023$) was associated with a higher risk of late death, right atrium right and left diameters (hazard ratio: 1.113; 95% confidence interval, 1.006–1.231; $P=0.038$) were associated with a higher risk of major adverse events.

Conclusion: Pulmonary endarterectomy is an effective way to treat CTEPH. Long-term outcome is excellent for patients who undergoing pulmonary endarterectomy who survived from peri-operation time. Postoperative mPAP is a significant prognostic factor for long-term death and right atrium right and left diameters is a significant prognostic factor for major adverse events. That shows patients with high postoperative mPAP and right atrium right and left diameter should be followed up closely.

Keywords

long-term outcomes, predictors, pulmonary endarterectomy, chronic thromboembolic pulmonary hypertension

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is classified into group 4 PH, which is a rare consequence of an acute pulmonary embolism.^{1,2} The main pathophysiology of CTEPH is pulmonary arterial obstruction by organized thrombotic material stemming from incompletely resolved acute pulmonary embolism.³⁻⁵ It was diagnosed as pulmonary hypertension with at least one segmental perfusion defect after at least 3 months of anticoagulation therapy.⁶ If untreated, patients with a mean pulmonary artery pressure (mPAP) higher than 40 mm Hg were reported to have a 5-year survival rate of less than 30%, and if it exceeds 50 mm Hg, the 5-year survival lowered to about 10%.^{7,8}

Pulmonary endarterectomy (PEA) is the preferred treatment for CTEPH patients which can significantly improve symptoms and pulmonary hemodynamics.⁹⁻¹¹ It has been used for over 30 years since the first PEA,¹² the surgical technology and procedures are being continuously improved over time so that surgical morbidity and mortality continues to decrease.¹³ The first PEA operation was done in 2002 in our center and has thus been performed for nearly 20 years until now. In this retrospective study, we reviewed our experience regarding effect, risk factors, long-term outcome of these CTEPH patients who underwent PEA.

In this study, we analyzed factors including basic clinical characteristics (sex, age, body mass index(BMI), smoking), symptoms (hemoptysis, dyspnea, venous thrombus embolism(VTE), WHO functional class), hemodynamics (PAP, pulmonary vascular resistance, cardiac index(CI)), echocardiography (right ventricular basal internal diameter, right atrium right and left diameter, left ventricular end-diastolic internal diameter) and so on.

Methods

Study Population

A retrospective review of our database identified consecutive 76 patients who underwent pulmonary artery endarterectomy for CTEPH and successfully discharged at Beijing Chao-yang hospital between December 2002 and December 2021.

The inclusion criteria for this operation included the following: (1) pulmonary hypertension with evidence of thromboembolic disease on pulmonary angiography, (2) absence of significant noncardiac comorbid disease. Patients with other

diseases (pulmonary sarcoma and other non-CTEPH patients) causing the same clinical and radiological appearance as CTEPH, missing cases during follow up and perioperative death were excluded from the analysis. Due to the retrospective nature of the study, informed consent was waived for data-analysis and publication under anonymized form (Figure 1).

Basic Clinical Characteristics and Hemodynamics

The diagnosis of CTEPH was performed using Swan-Ganz catheterization, computed tomography and pulmonary angiography in all cases. Evaluation of heart function using echocardiography and perfusion/ventilation scintigraphy was additionally applied to evaluate perfusion/ventilation mismatch. All patients had significant clinical symptoms, including palpitations, shortness of breath, and intolerance after exercise. Symptoms related to CTEPH were evaluated using WHO functional class and 6MWD preoperatively.

Surgical Procedure/ Surgery

The PEA procedure has been described previously.¹⁴ All PEA surgeries were conducted with a median sternotomy and deep hypothermia circulatory arrest (DHCA) with cardiopulmonary bypass (CPB). DHCA is limited to 20-min intervals, and usually one period is enough for the dissection to be completed on each side. The procedure is bilateral, and on completion of the right PEA, bypass is resumed and the patient reperfused while the arteriotomy is closed so that the procedure can be repeated on the left side, with circulatory arrest being initiated as necessary.¹⁵ Surgical related date is collected during surgery.

Follow-up and Study Endpoint

Follow-up data were obtained from hospital records and by means of direct telephone interviews with the patients or their families. Follow-up ended when the patient death or until December 2021. The primary follow-up endpoint of this study was all-cause mortality and the secondary endpoint was major adverse events (MAEs), defined as hospitalization resulting from balloon pulmonary angioplasty or giving pulmonary hypertension target medicine due to acute exacerbation.

Statistical Analysis

Continuous variables with a normal distribution are expressed as the mean \pm standard deviation (SD) and compared by Student's t-test, continuous variables with a non-normal distribution were presented as the median and interquartile (IQR) and compared by nonparametric test. Categorical variables are expressed as number with percent and compared by nonparametric test. Estimation of cumulative survival was performed by using the Kaplan–Meier method and compared with the log-rank test. To address factors that are associated with long-term mortality, the missing values impute by multiple imputation. Multivariate logistic regression analysis and Cox proportional hazards analysis were separately performed, respectively. Cox proportional

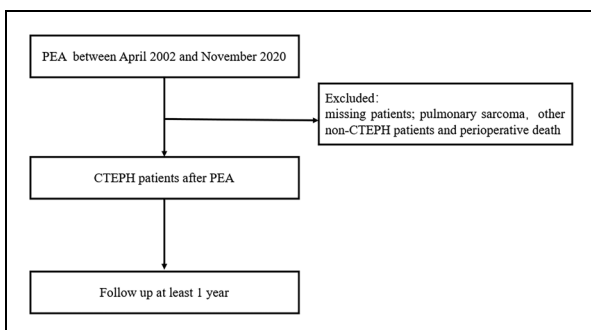


Figure 1. Study flow chart.

Table 1. Variables of Study Patients.

Variables	All (N = 76)	Late death		P Value	Major adverse events		P Value
		Yes(n = 7)	No(n = 69)		Yes(n = 10)	No(n = 66)	
Preoperative history							
Sex, (male, n%)	58(76.32)	6(85.71)	52(75.36)	1.000	6(60.00)	52(78.79)	0.366
Age, y	45.00 ± 11.52	35.86 ± 10.43	45.93 ± 11.28	0.027	52.20 ± 10.20	43.91 ± 11.38	0.033
BMI, kg/m ²	24.39 ± 2.90	23.10 ± 3.48	24.52 ± 2.83	0.221	23.59 ± 2.89	24.51 ± 2.90	0.357
Smoking, n%	39(51.32)	5(71.43)	34(49.28)	0.432	2(20.00)	37(56.06)	0.074
Albumin, g/L	36.67 ± 3.93	35.54 ± 4.10	36.79 ± 3.92	0.428	37.63 ± 4.34	36.53 ± 3.87	0.412
Lymphocyte count, 10 ⁹ /L	1.99(1.68–2.77)	2.07 ± 1.02	2.01(1.73–2.76)	0.461	1.81 ± 0.57	2.08(1.74–2.82)	0.115
NTproBNP, pg/ml	1115.00(504.95–2178.50)	1403.30 ± 950.97	1129.50(440.93–2167.25)	0.880	1187.83 ± 1083.53	1179.00(536.48–2167.25)	0.543
Therapeutic anticoagulant, n%	75(98.68)	7(100)	68(98.55)	1.000	10(100.00)	65(98.48)	1.000
PAH-specific drugs, n%	16(21.05)	1(14.29)	15(21.74)	1.000	4(40.00)	12(18.18)	0.246
Coronary artery bypass grafting, n%	3(0.04)	0(0.00)	3(4.35)	1.000	0(0.000)	3(4.55)	1.000
Symptoms at admission							
Time from symptoms to PEA, mo	36.00(21.00–60.00)	38.14 ± 37.48	36.00(21.50–60.00)	0.470	48.90 ± 32.50	36.00(20.25–60.00)	0.526
hemoptysis, n%	25(32.89)	4(57.14)	21(30.43)	0.209	3(30.00)	22(33.33)	1.000
dyspnea, n%	76(100)	7(100)	69(100)	1.000	10(100.00)	66(100.00)	1.000
6MWT, m	383.15 ± 105.13	336.25 ± 85.11	386.50 ± 106.25	0.360	355.71 ± 97.29	386.77 ± 106.45	0.467
WHO functional class(I–III/IV), n%	39/37(51.32/44.68)	3/4(42.86/57.14)	36/33(52.17/47.83)	0.414	2/8(20.00/80.00)	37/29(56.06/43.94)	0.074
VTE, n%	42(55.26)	3(42.86)	39(56.52)	0.694	5(50.00)	37(56.06)	0.719
Hemodynamics							
CI, L·min ⁻¹ ·m ⁻²	1.99(1.65–2.55)	1.51 ± 0.07	2.07(1.69–2.57)	0.044	2.77 ± 1.02	2.04 ± 0.67	0.089
sPAP, mm Hg	90.59 ± 20.30	79.57 ± 19.19	91.75 ± 20.20	0.132	98.40 ± 9.58	89.38 ± 21.29	0.034
dPAP, mm Hg	33.60 ± 8.19	31.86 ± 8.26	33.78 ± 8.23	0.558	32.60 ± 7.31	33.76 ± 8.37	0.681
mPAP, mm Hg	52.63 ± 10.63	47.76 ± 10.99	53.15 ± 10.55	0.196	54.53 ± 3.96	52.32 ± 11.34	0.254
PVR, dyn.s.cm ⁻⁵	908.50(741.00–1180.75)	1037.00 ± 334.37	908.50(738.75–1143.75)	0.747	900.78 ± 375.82	987.17 ± 332.05	0.478
Echocardiography							
Main pulmonary artery internal diameter, mm	32.04 ± 4.13	30.73 ± 5.75	32.17 ± 3.96	0.423	32.51 ± 4.75	31.96 ± 4.06	0.699
Left ventricular end-diastolic internal diameter, mm	39.68 ± 5.40	39.06 ± 7.23	39.75 ± 5.25	0.099	40.02 ± 4.12	39.63 ± 5.60	0.833
Left ventricular end-systolic internal diameter, mm	23.19 ± 5.01	21.73 ± 6.98	23.35 ± 4.80	0.377	23.66 ± 4.35	23.12 ± 5.13	0.753
Left ventricular end-systolic internal diameter, mm	72.00(67.00–76.00)	76.00 ± 9.29	71.90(67.00–76.00)	0.225	69.00(63.75–76.25)	72.00(68.00–76.50)	0.239

(continued)

Table 1. (continued)

Variables	All (N = 76)	Late death		P Value	Major adverse events		P Value
		Yes(n = 7)	No(n = 69)		Yes(n = 10)	No(n = 66)	
ejection fraction (LVEF), %							
Right ventricular basal internal diameter, mm	49.00(42.00–55.00)	44.00 ± 18.28	48.91 ± 7.68	0.013	50.63 ± 7.35	48.00(42.00–55.00)	0.522
Right atrium right and left diameters, mm	50.66 ± 9.60	55.76 ± 9.11	50.12 ± 9.56	0.141	54.90 ± 9.66	49.99 ± 9.50	0.134
Estimated of pulmonary artery systolic pressure, mm Hg	95.45 ± 21.75	100.26 ± 24.51	94.94 ± 21.59	0.797	100.05(97.63–107.25)	94.26 ± 21.65	0.265
Postoperative Albumin, g/L	37.45(34.38–42.63)	34.77 ± 5.92	37.90(24.40–43.10)	0.095	35.55 ± 4.07	38.20(34.40–43.15)	0.075
Lymphocyte count, 10 ⁹ /L	1.37(1.03–1.60)	1.29 ± 0.62	1.36(1.04–1.63)	0.512	1.27 ± 0.35	1.42 ± 0.50	0.354
Postoperative sPAP, mm Hg	49.00(40.25–60.00)	67.00 ± 17.79	47.00(39.00–60.00)	0.418	60.00(59.00–68.00)	47.00(39.00–59.00)	0.014
Postoperative dPAP, mm Hg	20.69 ± 6.34	25.71 ± 8.18	20.13 ± 5.93	0.026	24.50 ± 9.06	20.19 ± 5.83	0.227
Postoperative mPAP, mm Hg	30.00(24.58–37.33)	39.48 ± 10.44	29.67(24.33–36.33)	0.019	38.00 ± 12.69	30.07 ± 7.98	0.016
Postoperative PVR, dyn·s·cm ⁻⁵	155.00(127.00–241.75)	218.33 ± 136.40	156.00(127.00–239.50)	0.773	251.20 ± 138.76	154.00(127.00–221.00)	0.504

Categorical data are presented as n (%) and continuous data as mean ± standard deviation or median and interquartile.

BMI: body mass index; PEA: pulmonary endarterectomy; VTE: venous thromboembolism; 6MWD: 6 min walking distance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; CI: cardiac index; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance.

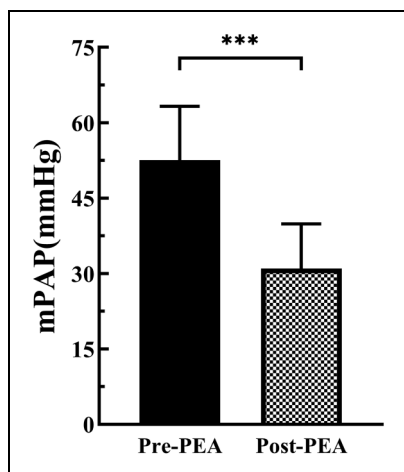


Figure 2. Change of mPAP and PVR.

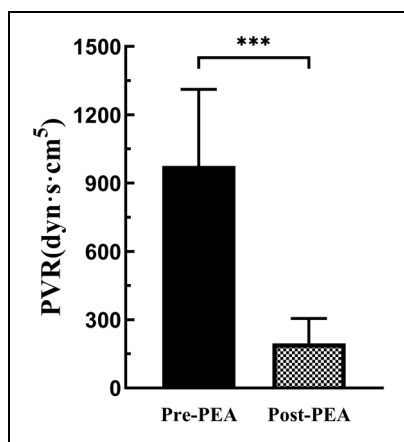


Figure 3. Change of mPAP and PVR.

hazards analysis was performed at the time point of 1, 3, 5, 15 years after surgery, and at the end of the follow-up period (overall). The optimal postoperative mPAP cutoff value for adverse events were determined with the aid of a receiver operating characteristic curve. $P < 0.05$ are considered statistically significant. All statistical analyses were performed with GraphPad Prism Version 8 (GraphPad Software, La Jolla, CA) and SPSS 26.0 software (IBM, Armonk, NY).

Results

Clinical Characteristics of Enrolled Patients

Baseline characteristics, preoperative hemodynamic and echocardiographic data are shown in Table 1. The average age of the patients was 45.00 ± 11.52 years, and 76.32% were male. Before surgery, 16 patients require pulmonary arterial hypertension-targeted treatments. The time from first symptoms to PEA was $36.00(21.00-60.00)$ months. All patients suffered from clinical symptoms preoperatively, there are 37(44.68%)

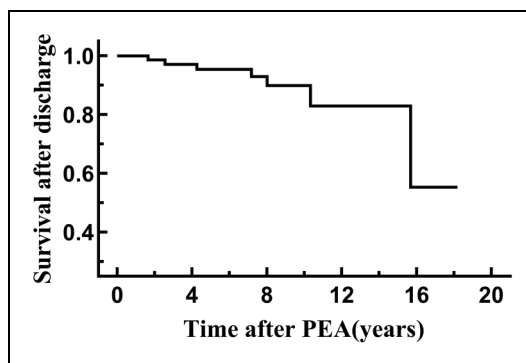


Figure 4. Kaplan–Meier survival curves in patients with operated chronic thromboembolic pulmonary hypertension (CTEPH).

patients classified to WHO class III or IV and 42(55.26%) patients had VTE history.

Hemodynamics at diagnosis showed that mPAP was 52.63 ± 10.63 mm Hg and PVR was $908.50(741.00-1180.75)$ $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$, CI was $1.99(1.65-2.55)$ $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-1}$.

Echocardiography findings showed that the main pulmonary artery Internal diameter was 32.04 ± 4.13 mm, right ventricular basal internal diameter was $49.00(42.00-55.00)$ mm (Table 1).

Long-Term Survival

As shown in Figures 2, 3, the mPAP and PVR were significantly decreased after the surgery. And follow-up ended with interval of $7.29(4.00-8.97)$ years. The longest follow-up period was 18 years and the shortest was 1 year. The survival rate after PEA at 1,3,5,10,15 years was 100%, 97.10%, 95.40%, 89.80% and 82.90%, respectively (Figure 4). After the surgery, all patients received oral anticoagulant therapy. Four patients require pulmonary arterial hypertension-targeted treatments, 9 patients received balloon dilatation of pulmonary artery (BPA).

Age (35.86 ± 10.43 VS 45.93 ± 11.28 ; $P = 0.027$) was much younger in those patients died compared with the patients survived. Preoperative CI (1.51 ± 0.07 VS $2.07(1.69-2.57)$, $P = 0.044$) was much lower in those patients died compared with the patients survived. Preoperative right ventricular basal internal diameter (44.00 ± 18.28 VS 48.91 ± 7.68 , $P = 0.013$) was much lower in those patients died compared with the patients survived. Postoperative dPAP (25.71 ± 8.18 VS 20.13 ± 5.93 , $P = 0.026$) and mPAP (39.48 ± 10.44 VS $29.67(24.33-36.33)$; $P = 0.019$) was much higher in those patients died compared with the patients survived (Table 1).

Major Adverse Events

The incidence of MAEs is 13.16% (10/76). Age (52.20 ± 10.20 VS 43.91 ± 11.38 ; $P = 0.033$) was higher in those patients occurred MAEs compared with the patients no MAEs occurred. Right atrium right and left diameters (54.90 ± 9.66 VS 49.99 ± 9.50 ; $P = 0.134$) has no significant difference in those patients.

Table 2. Predictors for Late Death and Endpoint Event After Pulmonary Endarterectomy.

Variables	Univariate analysis			Multivariate analysis			Sex adjustment		
	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Late death									
Age, y	0.924	0.859–0.995	0.036	0.894	0.805–0.988	0.028	0.898	0.809–0.997	0.045
Albumin, g/L	0.917	0.742–1.134	0.424						
WHO functional class(I-II/III-IV)	1.871	0.552–6.343	0.315						
CI, L·min ⁻¹ ·m ⁻²	0.193	0.023–1.592	0.127	1.040	0.084–12.897	0.974	1.252	0.208–7.531	0.803
Right ventricular basal internal diameter, mm	0.939	0.841–1.049	0.267						
Right atrium right and left diameters, mm	1.062	0.979–1.152	0.147	0.534	0.921–1.173	0.534	0.993	0.863–1.142	0.917
Perioperative mPAP, mm Hg	0.949	0.875–1.029	0.203	0.864	0.751–0.994	0.042	1.016	0.925–1.116	0.732
Postoperative mPAP, mm Hg	1.116	1.018–1.222	0.190	1.208	1.047–1.389	0.012	1.144	1.018–1.285	0.023
Major adverse events									
Age, y	1.077	1.003–1.156	0.041	1.073	0.969–1.187	0.174	0.245	0.030–2.003	0.189
Smoking, %	5.103	1.006–25.890	0.049						
CI, L·min ⁻¹ ·m ⁻²	3.100	1.184–8.118	0.021	4.266	0.863–21.092	0.074	3.707	0.668–20.572	0.130
WHO functional class(I-II/III-IV)	0.196	0.039–0.994	0.049	0.192	0.028–1.309	0.092	0.152	0.019–1.237	0.078
Right atrium right and left diameters, mm	1.054	0.983–1.131	0.138	1.093	0.990–1.206	0.077	1.113	1.006–1.231	0.038
mPAP, mm Hg	1.020	0.958–1.085	0.540						
Postoperative mPAP, mm Hg	1.097	1.009–1.192	0.030	1.105	0.971–1.257	0.130	1.092	0.959–1.243	0.185

HR: hazard ratio; 95%CI: 95%confidence interval BMI: body mass index; CI: cardiac index; mPAP: mean pulmonary artery pressure.

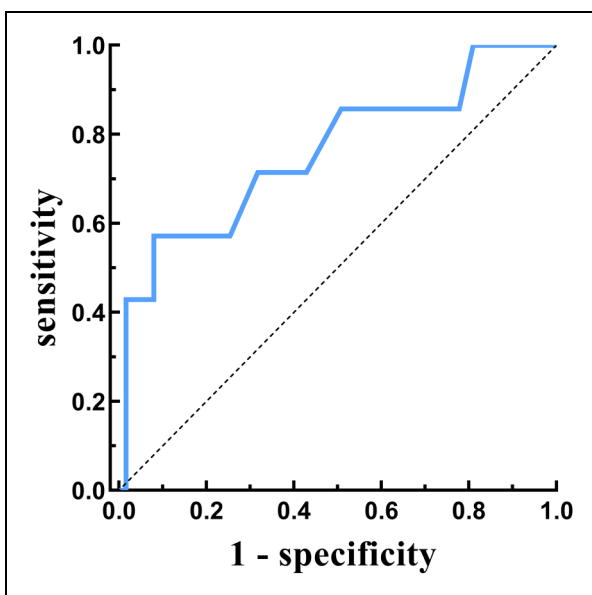


Figure 5. The receiver operating characteristic curve to predict all-cause mortality after surgery.

And postoperative mPAP (38.00 ± 12.69 VS 30.07 ± 7.98 ; $P = 0.016$) was much higher in those patients with MAEs (Table 1).

Multivariate Logistic Regression

Multivariate logistic regression analysis showed that age, perioperative mPAP and postoperative mPAP were predictors in late death. After adjusted for sex, age (HR:0.898, 95%CI:0.809–0.997, $P = 0.045$) and postoperative mPAP (HR:1.144, 95%CI:1.018–1.285, $P = 0.023$) were independent predictors in late death (Table 2). Postoperative mPAP (HR:1.145, 95%

CI:1.041–1.259, $P = 0.005$) was an independent predictor in primary endpoint event. After adjusted for sex, right atrium right and left diameters (HR:1.133, 95%CI:1.006–1.231, $P = 0.038$) was an independent predictor in MAEs.

The cut-off value was determined with ROC curve and Youden index. ROC curve analysis indicated that postoperative mPAP 40.50mm Hg was a cut off value of death ($P = 0.019$; the area under the ROC curve was 0.771) (Figure 5).

Discussion

This is the first study evaluating nearly 20 years outcomes of CTEPH patients after PEA in China. The results of this retrospective analysis demonstrate the prognostic impact of long-term outcomes, which can provide a reference for PEA treatment.

PEA is the preferred treatment of choice for operable patients with CTEPH with excellent long-term outcome.^{9,16,17} During a recent study in France, PVR, CO and TL_{CO} can predict postoperative outcomes.¹⁸ In our study, age, perioperative mPAP, postoperative mPAP were significant predictors for death. However, after sex and age adjustment, only postoperative is an independent predictor for death. This suggests that not only postoperative status can affect the outcome.

It was observed that postoperative mPAP can affect late death. There has been an imaging data of pulmonary vascular study indicating that 20% of the pulmonary vasculature abnormal with new vascular lesions involved even with regular anticoagulation therapy.^{19,20} This demonstrates that residual PH remains an important factor in the survival. In our center, the incidence of residual pulmonary hypertension was 22.4%. In this study, we calculate mPAP = 40.5mm Hg is the cutoff value for postoperative death. In ERS statement on CTEPH, mPAP ≥ 38mm Hg can affect the patient long-term outcome,

mPAP>30mmHg as a suggest threshold to initiate drug therapy.⁹

The incidence of VTE varied in different studies, especially in CTEPH cohort. The incidence of DVT in a UK registry study was 59.3% to 60.4% in PEA patients. The incidence of PE/DVT is 63.8/48.3, 69.8/36.7, 39.1/43.5% respectively in America, Europe and Japan in the worldwide prospective CTEPH Registry.²¹ The incidence of VTE was 55.26% in our study, within the scope of reported literatures.

A small number of studies have considered that elderly patients should be offered PEA in expert center.^{22,23} In a recent study, the patients were split into three groups according to their age: group1: ≤50 years, group2: >50≤70 years, group3: >70 years, they find that survival of the group1 patients were better than group2 patients and group2 patients were better than group3 patients with 5 years follow up.²⁴ In our center, the age is an independent risk factor of long-term outcome, and all-cause mortality patients were younger, this may be relevant to older patients received BPA and drug treatment. In our center, one patient was very young at the time of the operation, and dead after about 10 years, because this patient has patent foramen ovale and drugs abuse history. This may influence the results on age.

This study is a retrospective observational design. There are several limitations: 1) Sample sized is limited. 2) The follow-up time varies too much between different patients. 3) For the limitation of target medicine, only 16 patients received pulmonary arterial hypertension-targeted treatments before PEA and 4 patients received pulmonary arterial hypertension-targeted treatments after PEA 4) Previous studies suggest that sex-related survival difference in CTEPH patients who underwent PEA, there are more males than females in PEA patients in our center, this may affect the all-cause mortality rate.

Conclusion

In conclusion, our study shows that PEA can improve hemodynamic effectively and the patients have excellent long-term prognosis. And residual pulmonary hypertension can affect the survival of patients.

Acknowledgements

Not applicable

Author Contributions

Shuai Sun and Ji-Feng Li conceived and designed the research and acquired the data. Jia-Yu Liu and Lin Liu performed statistical analyzes. Ran Miao Su-Qiao Yang, Tu-Guang Kuang, Juan-Ni Gong, Song Gu, Yan Liu contributed to the interpretation of data. Shuai Sun and Ji-Feng Li drafted the manuscript. Yuan-Hua Yang made critical revision of the manuscript for key intellectual content and have seen and approved the final version.

Consent for Publication

All authors have viewed the manuscript and written informed consent for publication was obtained from all participants.

Data Availability

The data will not be shared, because the identified participants information is included in the data.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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