J Chin Med Assoc

ORIGINAL ARTICLE

The long-term outcome of chronic thromboembolic pulmonary hypertension: Pulmonary endarterectomy and balloon pulmonary angioplasty

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Abstract

Background: The long-term outcome on patients with chronic thromboembolic pulmonary hypertension (CTEPH) has not been ideal after standard medical treatment. However, good outcome for patients with CTEPH after interventions such as pulmonary endarterectomy (PEA) and balloon pulmonary angioplasty (BPA) has been reported recently. The aim of this study was to evaluate the impact of PEA or BPA on long-term outcomes for CTEPH patients in Han-Chinese population.

Methods: This was a multicenter, prospective case-control study. Patients with CTEPH were enrolled between January, 2018 and March, 2020. They were divided into two groups, including intervention (PEA or BPA) and conservative groups. The followed-up period was 26 months after treatment. The endpoints were all-cause mortality and CTEPH mortality.

Results: A total of 129 patients were enrolled and assigned to receive PEA/BPA (N = 73), or conservative therapy (N = 56). Overall, the 26-month survival rate of all-cause mortality was significantly higher in intervention group compared to that in conservative group (95.89% vs 80.36%; log-rank $p = 0.0164$). The similar trend was observed in the 26-month survival rate of CTEPH mortality (97.26% vs 85.71%; log-rank $p = 0.0355$). Regarding Cox proportional-hazard regression analysis, the hazard ratios (HRs) on patients with CTEPH receiving intervention in the outcome of all-cause mortality and CTEPH mortality were statistically significant (HR = 0.07 and $p = 0.0141$ in all-cause mortality; HR = 0.11 and $p = 0.0461$ in CTEPH mortality).

Conclusion: This multicenter prospective case-control study demonstrated that intervention such as PEA and BPA increased the long-term survival rate for patient with CTEPH significantly. Intervention was an independent factor in long-term outcome for patients with CTEPH, including all-cause mortality and CTEPH mortality.

Keywords: Balloon pulmonary angioplasty; Chronic thromboembolic pulmonary hypertension; Long-term outcome; Pulmonary endarterectomy

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2024) 87: 273-279.

Received August 13, 2023; accepted December 3, 2023.

doi: 10.1097/JCMA.0000000000001059

1. INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH), classified group 4 pulmonary hypertension (PH), is characterized by obstruction of the pulmonary vasculature by organized thromboembolic material and vascular remodeling due to previous pulmonary embolism (PE).[1] Poor prognosis for CTEPH such as right heart failure and death can occur if patients with CTEPH do not receive appropriate management.[2] According to Kim et al[1], a 3-year survival rate for patients with CTEPH receiving medical treatment was 70%. It is critical to target those patients and provide appropriate management.

According to 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis of PH,[3] CTEPH should be considered in patients with associated symptoms of PH and PE history. Various diagnostic techniques for CTEPH, including echocardiography, right heart catheterization (RHC), pulmonary angiography, tomographic pulmonary angiography (CTPA), and ventilation/perfusion (V/Q) scans, should be provided to target these patients. The diagnostic criteria for CTEPH were as follows: (1) any mismatched perfusion defects in the V/Q scan and intermediate/high probability of PH detected by echocardiography; and (2) specific diagnostic signs for CTEPH detected by CTPA and RHC.

Several management strategies have been provided for patients with CTEPH, including pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA), and PH-targeted medical therapy.[4] In 2016, Delcroix et al reported that a 3-year survival rate of patients with operatable CTEPH was 89%, and a high long-term survival rate of patients with CTEPH who were treated with BPA has also been identified in previous studies.[5–7] Compared to medical treatment only for CTEPH patients, invasive intervention seems to provide better outcomes in patients with CTEPH. However, long-term outcomes of patients with CTEPH who have undergone interventions in Taiwan are inconclusive. Thus, our study aimed to estimate the long-term impact of this intervention in CTEPH patients.

2. METHODS

2.1. Study design and patient selection

This was a multicenter, prospective case-control study. Patients diagnosed with CTEPH at six medical centers in Taiwan (National Taiwan University Hospital, Cheng Hsin General Hospital, Mackay Memorial Hospital, China Medical University Hospital, National Cheng Kung University Hospital, and Kaohsiung Veterans General Hospital) between January 2018 and March 2020 were enrolled in this study. The diagnostic protocol was based on the CTEPH guidelines[8] and these enrolled patients received standard medical treatment for CTEPH once the diagnosis was confirmed. Standard medical treatment included anticoagulant drugs such as vitamin K antagonist (VKA) and novel oral anticoagulant (NOAC), soluble guanylyl cyclase (sGC) stimulators, PDE-5 inhibitors, endothelin receptor antagonists, and prostanoid therapy. After assessing patients' condition, their doctors would decide what kinds of treatment were available to them. Basically, patients were treated with invasive interventions, such as PEA and BPA, or without interventions. The intervention and nonintervention groups were defined as intervention and conservative groups, respectively. Parameters associated with disease severity were demonstrated, including World Health Organization (WHO) functional class (Fc), b-type natriuretic peptide (BNP), left ventricular ejection fraction, mean pulmonary arterial pressure, N-terminal pro-BNP (NT-proBNP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance, and 6-minute walk test.

The Research Ethics Committee of all hospitals reviewed and approved this study (ClinicalTrials.gov Identifier: NCT03667391), and informed consent was obtained from all patients.

The outcomes of our study were defined as all-cause death and CTEPH death in the enrolled patients with CTEPH with or without intervention. Each enroller was followed up as an outpatient and by telephone visits after starting treatment for CTEPH and the reasons for death were identified from medical records.

2.2. Statistical analysis

Clinical data on comorbidities, diagnostic procedures for CTEPH, types of invasive procedures for CTEPH, pulmonary arterial hypertension-targeted medicine use, and clinical follow-up visits were retrieved from the medical records. The statistical analysis system version 9.4 software (SAS Institute Inc., Cary, NC) was used for all analyses. Descriptive statistics were calculated for all variables, with categorical data reported as percentile values and continuous variables reported as means and SDs. Between-group differences were evaluated by paired t test for continuous variables and chi-squared test for categorical variables, with statistical significance being set at $p < 0.05$. Kaplan-Meier cumulative survival curves were constructed to compare the survival of patients with CTEPH with and without PEA or BPA treatment. Log-rank test with a $p < 0.05$ were considered statistically significant. Cox proportional hazards regression analysis was used to calculate the hazard ratio (HR), and associated 95% CIs, for significant variables. A p value for interaction <0.05, indicating significant differences between subgroups.

3. RESULTS

In total, 129 patients with CTEPH were enrolled in our study. Basic patient characteristics, diagnoses, hemodynamics, and treatments are shown in Table 1. A total of 73 and 56 patients were enrolled in the intervention and conservative groups, respectively. The patients in the intervention group were younger than those in the conservative group (57.7 vs 67.1 years, $p < 0.001$). Moreover, there was a higher proportion of severe function classes (WHO Fc: III + IV) in the intervention group than in the conservative group (83.6% vs 58.9%, $p = 0.002$). In addition, the PCWP in the intervention group was lower than that in the conservative group (11.67 vs 15.06 mm Hg, $p = 0.004$). For other variants, there were no significant differences between the two groups.

The clinical signs, comorbidities, and risk factors of patients are shown in Table 2. The most common clinical sign was dyspnea, followed by exercise intolerance, and lower leg edema. The most common comorbidity was hypertension, followed by acute PE, and dyslipidemia. The proportion of dyslipidemia in the intervention group was higher than that in the conservative group (19.18% vs 37.5%, $p = 0.02$). The remaining variants in the two groups were not statistically different.

Kaplan-Meier cumulative curves were used to evaluate the survival rates of patients with CTEPH with or without PEA or BPA. Regarding all-cause death outcome, the survival rate was higher in the intervention group than in the conservative group (log-rank $p = 0.0164$, Fig. 1). The 26-month survival rate of patients with CTEPH in the intervention group was 95.89%. In contrast, the 26-month survival rate in the conservative group was 80.36%. Regarding the CTEPH death outcome, the 26-month survival rate in the intervention group was 97.26%, and that in the conservative group was 85.71% (log-rank $p = 0.0355$, Fig. 2).

Cox proportional-hazard regression analysis, the multivariate analysis, was performed, and the forest plot of HR of subgroup analysis for all-cause death outcome is illustrated in Fig. 3. The PEA or BPA management was indicated as an independent variant to the all-cause death outcome on patients with CTEPH (HR = 0.07; 95% CI, 0.01-0.59; $p = 0.02$). According to the outcome of CTEPH death, PEA or BPA was also shown as an independent variant (HR = 0.11; 95% CI, 0.01-0.59; $p = 0.0461$, Fig. 4). With regard to other subgroups including gender, age ≥65 years, body mass index (BMI) ≥30, severe WHO fc (III + IV), and BNP >300 ng/L, other comorbidities such as PE, chronic obstructive pulmonary disease, and diabetes, and medical treatment including VKA, NOAC, and sGC simulator, all-cause death and CTEPH death outcomes were not statistically affected.

Table 1

Basic characteristics, diagnosis, hemodynamics, and treatment for CTEPH patients

	Intervention group	Conservative group	
	n = 73	n = 56	*p*
Basic characteristics			
Age, y	57.7 ± 16.2	67.1 ± 14.8	<0.001
Male	22 (30.1%)	13 (23.3%)	0.038
Body height, cm	159.9 ± 10.0	157.2 ± 10.3	0.125
Body weight, kg	63.8 ± 14.0	63.6 ± 14.9	0.950
Body mass index	24.88 ± 4.5	25.81 ± 5.8	0.319
Initial WHO functional class			<0.001
I+II	12 (16.4%)	23 (41.1%)	
III+IV	61 (83.6%)	33 (58.9%)	0.002
Diagnosis			
Echocardiography	69 (94.5%)	56 (100%)	0.132
CTA	72 (98.6%)	55 (98.2%)	1.000
Ventilation/perfusion scan	59 (80.8%)	48 (85.7%)	0.231
Right heart catheterization	72 (98.6%)	55 (98.2%)	1.000
6MWT, m	312.2 ± 129.3	329.4 ± 115.4	0.873
NT-proBNP, pg/mL	1942.7 ± 3215.1	1453.2 ± 2618.7	0.519
BNP, pg/mL	1326.1 ± 3290.7	839.5 ± 2300.7	0.622
D-dimer, ng/mL	1434.4 ± 3127.3	459.1 ± 1218.0	0.099
Hemodynamics			
Mean PAP, mm Hg	43.89 ± 12.05	39.76 ± 11.80	0.057
PCWP, mm Hg	11.67 ± 5.32	15.06 ± 6.95	0.004
PVR, dyn.s.cm^{-5}	9.16 ± 4.77	31 ± 120.81	0.198
Cardiac output, L/min	4.25 ± 1.58	3.91 ± 1.37	0.214
Cardiac index, L/min/m^2	2.54 ± 0.86	2.38 ± 0.77	0.298
Treatment			
Vitamin K antagonists	44 (60.2%)	24 (42.8%)	0.041
Novel oral anticoagulant			
Rivaroxaban	24 (32.8%)	33 (58.9%)	0.044
Dabigatran	1 (1.3%)	0 (0%)	
Edoxaban	1 (1.3%)	1 (1.7%)	
Apixaban	15 (20.5%)	5 (8.9%)	
Others	0 (0%)	1 (1.7%)	
No used	31 (42.4%)	16 (28.5%)	
PH medications			
sGC stimulator or PDE-5 inhibitor	66 (90.4%)	44 (78.5%)	0.060
Endothelin receptor antagonist	4 (5.4%)	2 (3.5%)	0.069
Prostacyclins	2 (2.7%)	1 (1.7%)	1.000

Continuous data are shown as mean ± standard deviation and categorical data are shown as number (%).

6MWT = 6-minute walk test; BNP = b-type natriuretic peptide; CTEPH = chronic thromboembolic pulmonary hypertension; CTA = Computed tomography angiography; CI = cardiac index; CO = cardiac output; LVEF = left ventricular ejection fraction; mean PAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal pro-b-type natriuretic peptide; PDE-5 inhibitor = phosphodiesterase type 5 inhibitor; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; sGC stimulator = soluble guanylate cyclase stimulator.

4. DISCUSSION

This multicenter study was the first to compare the long-term outcomes of patients with CTEPH with or without intervention in the Han-Chinese population. A higher survival rate was observed in patients with CTEPH who underwent intervention. Because several diagnostic tools for CTEPH have been recently applied to identify patients, the epidemiology of CTEPH and long-term outcomes of intervention can be properly established.

4.1. Epidemiology, hemodynamics, and mortality of CTEPH

The prevalence of CTEPH according to sex remains inconsistent worldwide. Pepke-Zaba et al[9] reported the prevalence of CTEPH was equal in men and women. Liu et al[10] reported that the incidence of CTEPH was female predominant (70.6%) in Taiwan. In contrast, the female on male ratio was 0.7 in the American group reported by Nakamura et al.[11] The prevalence of CTEPH in our study is female predominant, which is consistent with Liu's study and it may be the population from the same country.

According to previous studies conducted in different countries,[4,12,13] the long-term survival rate of patients with CTEPH who do not undergo invasive interventions is relatively poor. A 3-year survival rate for nonoperative patients with CTEPH was 74.3% according to Taniguchi et al.[12] According to Delcroix et al,[4] the 3-year survival rate for nonoperative patients was 70%. The 1- and 3-year survival rates were 82% and 70%, respectively, for patients with CTEPH according to Condliffe et al.[13] In the present study, the 26-month survival rates of patients with CTEPH in the conservative group were 80.36% and 85.71%, respectively (Figs. 1 and 2). As a result, medical treatment only for patients does not seem to provide an ideal long-term outcome and the 20% to 30% of mortality rates within 3 years.

4.2. The impact of PEA and BPA on long-term outcomes in patients with CTEPH

According to Dardi et al,[14] CTEPH can be cured by PEA; thus, PEA is recommended as the first-line treatment for patients with CTEPH. Good long-term outcomes and high survival rates in

Table 2

Clinical sigs, comorbidities, and risk factors for CTEPH patient

Clinical signs	Intervention group n = 73	Conservative group n = 56	*p*
Chest pain	10 (13.7%)	9 (16.07%)	0.706
Cyanosis	2 (2.74%)	1 (1.79%)	1.000
Dizziness	7 (9.59%)	12 (21.43%)	0.060
Dyspnea	64 (87.67%)	51 (91.07%)	0.538
Exercise intolerance	36 (49.32%)	26 (46.43%)	0.745
Fatigue	16 (21.92%)	8 (14.29%)	0.269
Lower leg edema	18 (24.66%)	24 (42.86%)	0.028
Syncope	5 (6.85%)	9 (16.07%)	0.095
Others	11 (15.07%)	8 (14.29%)	0.901
Comorbidities			
Acute pulmonary embolism	19 (26.03%)	18 (32.14%)	0.446
Acute coronary syndrome	0 (0.0%)	0 (0%)	-
COPD	2 (2.74%)	6 (10.71%)	0.076
Diabetes	11 (15.07%)	11 (19.64%)	0.493
Dyslipidemia	14 (19.18%)	21 (37.5%)	0.020
Hypertension	21 (28.77%)	25 (44.64%)	0.062
Ischemic heart disease	2 (2.74%)	3 (5.36%)	0.652
Left-sided heart failure	1 (1.37%)	3 (5.36%)	0.316
Other disease of endocardium	5 (6.85%)	5 (8.93%)	0.273
Other lung diseases	5 (6.85%)	7 (12.5%)	0.273
Other chronic pulmonary heart disease	4 (5.48%)	0 (0%)	0.132
Sleep apnea	2 (2.74%)	1 (1.79%)	1.0
Stroke	0 (0%)	1 (1.79%)	0.434
Transient ischemia attack	0 (0%)	0 (0%)	-
Others	10 (13.7%)	14 (25%)	0.121
Risk factors			
Pulmonary embolism	62 (84.93%)	45 (80.3%)	0.791
Antiphospholipid syndrome/Lupus anticoagulant	6 (8.22%)	3 (5.3%)	0.527
Coronary disease or myocardial infarction	6 (8.22%)	10 (17.8%)	0.125
Family history of DVT or PE	1 (1.37%)	0 (0%)	0.668
Fracture	3 (4.11%)	3 (5.36%)	1.0
Hemolytic anemia	2 (2.74%)	4 (7.14%)	0.402
Infection of ventriculoarterial shunt or pacemaker	0 (0%)	0 (0%)	-
Inflammatory bowel disease	0 (0%)	3 (5.36%)	0.079
Malignancy	5 (6.85%)	6 (10.71%)	0.530
Type 2 diabetes mellitus	11 (15.07%)	11 (19.64%)	0.493
Obesity (BMI ≥ 30 kg/m^2)	11 (15.07%)	7 (12.50%)	0.676
Previous major surgery	15 (20.55%)	8 (14.29%)	0.357
Smoking	14 (19.18%)	6 (10.71%)	0.188
Splenectomy	5 (6.85%)	0 (0%)	0.068
Thyroid disorder and hormone replacement therapy	8 (10.96%)	6 (10.71%)	0.964
Major trauma	0 (0%)	1 (1.79%)	0.434
Varicose veins	5 (6.85%)	1 (1.79%)	0.232
DVT	19 (26.03%)	11 (19.64%)	0.394
Systemic-pulmonary shunt	0 (0%)	4 (7.14%)	0.033

Categorical data are shown as number (%).

- is indicated as cannot be compared due to the value in two groups were 0%.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; PE = pulmonary embolism.

patients with CTEPH receiving PEA have also been reported in previous studies.[15–17] A mortality rate of 3% to 7% at 3 to 12 months after PEA was reported in a study by Mayer et al.[15] According to Cannon et al,[16] the survival rate and quality of life were also improved in patients with CTEPH patients receiving PEA. A 3-year survival rate of 88% to 91% in patients with CTEPH receiving PEA was reported by Saouti et al.[17] However, the risks and possible complications of PEA should be evaluated cautiously. The mortality rate for patients with PEA is between 4% and 24%.[18] As a result, operatable patients with CTEPH could be considered for PEA treatment early after cautiously assessing their clinical condition. BPA is another option for patients with in-operable CTEPH. Improvements in hemodynamics, symptoms, and exercise capacity in patients with CTEPH after BPA have been reported in several studies in Japan.[5,6,19] Inami et al[6] reported that the 3- and 5-year survival rates of patients with CTEPH who underwent BPA were 98.0% and 95.5%, respectively. Safety and improvement in quality of life and pulmonary hemodynamics were also reported by Hoole et al[20] in the UK. Furthermore, 0% to 3.4% mortality rate of patients with CTEPH undergoing BPA has been reported in previous studies.[21,22] According to the low mortality rate of BPA and good outcome in patients with CTEPH, BPA should be considered as an alternative treatment for in-operable patients. In

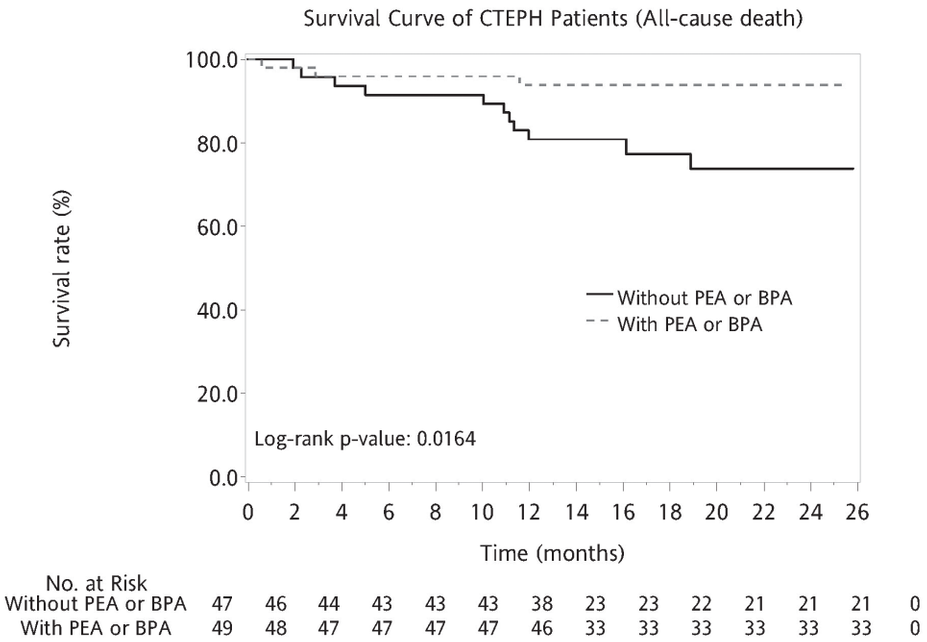

Fig. 1 Kaplan-Meier survival curve of all-cause death of CTEPH patients with PEA or BPA and without intervention. Overall, the 26-mo survival rate was higher on patients with PEA or BPA (95.9% vs 80.4%, $p = 0.0164$) compared to patients without intervention. BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PEA = pulmonary endarterectomy.

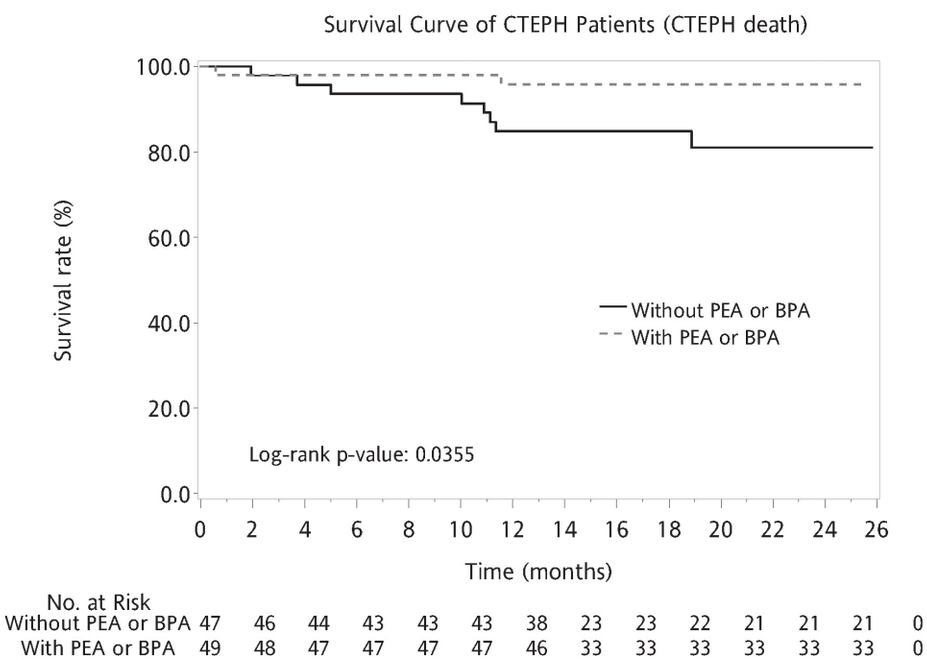

Fig. 2 Kaplan-Meier survival curve of CTEPH death on chronic CTEPH patients with PEA or BPA and without intervention. The 26-mo survival rate of CTEPH death was higher on patients with PEA or BPA (97.3% vs 85.7%, $p = 0.0355$). BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PEA = pulmonary endarterectomy.

the present study, higher 26-month survival rates were identified in the intervention group for all-cause death and CTEPH death outcomes (95.89% vs 97.26%) (Figs. 1 and 2). A statistically significant difference in the survival rate of all-cause death and CTEPH death was detected between the two groups ($p = 0.0164$ vs $p = 0.0355$). The survival rate on patients with CTEPH in the present study was similar to that reported in previous studies worldwide. Furthermore, the results of the Cox proportional hazard regression analysis showed that intervention was an independent variant of the mortality in patients with CTEPH. Patients with CTEPH in the intervention group had better all-cause death outcome and CTEPH death outcome, respectively (HR = 0.07 vs HR = 0.11) (Figs. 3 and 4). Moreover, BMI, age, and BNP are considered as significant risks for death of CTEPH

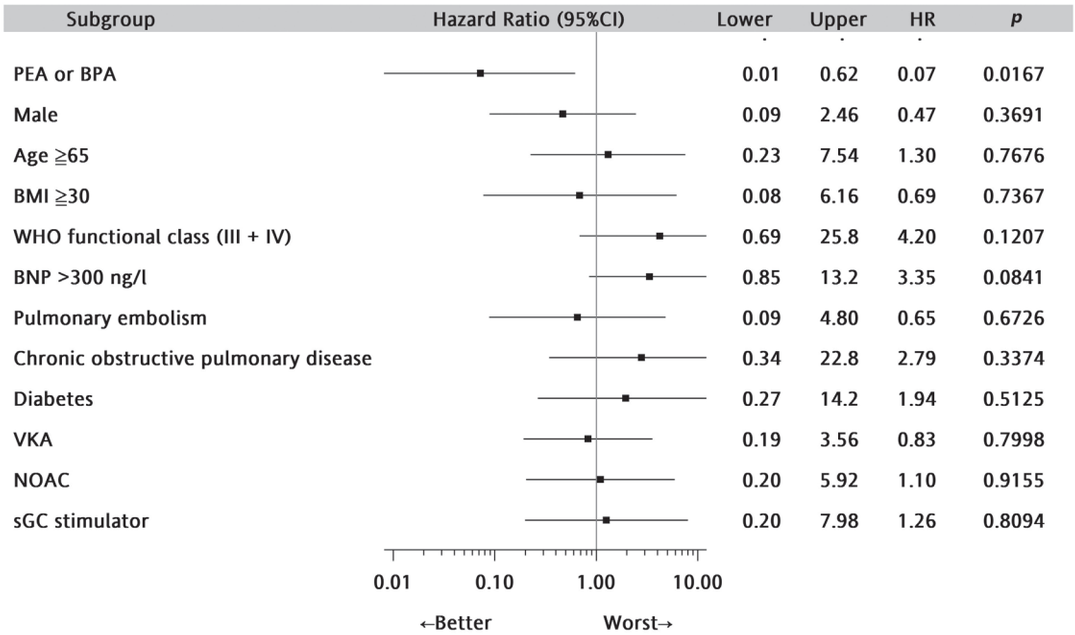

Fig. 3 Forest plot of HR and 95% CI of subgroup analysis in all-cause death outcome. Pulmonary endarterectomy or balloon pulmonary angioplasty was the independent variant to all-cause death outcome on CTEPH patients (HRs = 0.07 and $p = 0.0142$). The rest of factors including BMI ≥30, age ≥65, BNP >300, comorbidities, and medical treatments which are associated with possible CTEPH prognosis and mortality, had no statistical difference. BMI = body mass index; BNP = b-type natriuretic peptide; CTEPH = chronic thromboembolic hypertension patients; HR = hazard ratios; NOAC = novel oral anticoagulant; VKA = vitamin K antagonist; WHO = World Health Organization.

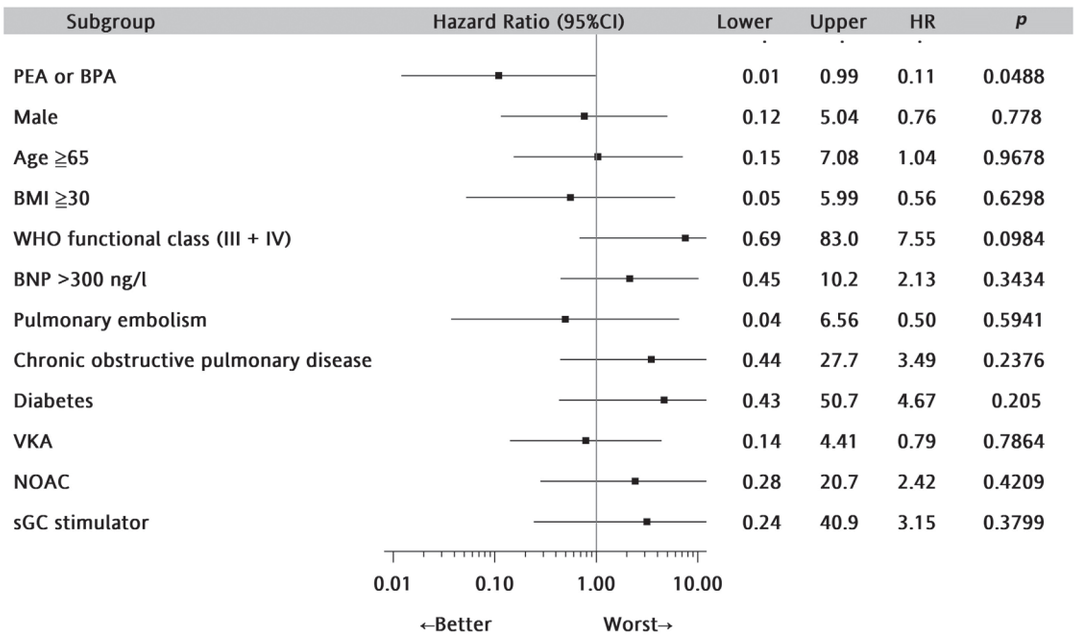

Fig. 4 Forest plot of HR and 95% CI of subgroup analysis in CTEPH death outcome. Pulmonary endarterectomy or balloon pulmonary angioplasty was the independent variant to CTEPH death outcome on CTEPH patients (HR = 0.11 and $p = 0.0461$). The rest of factors including BMI ≥30, age ≥65, BNP >300, comorbidities, and medical treatments which are associated with possible CTEPH prognosis and mortality, had no statistical difference. BPA = balloon pulmonary angioplasty; BMI = body mass index; BNP = b-type natriuretic peptide; CTEPH = chronic thromboembolic hypertension patients; HR = hazard ratios; NOAC = novel oral anticoagulant; PEA = pulmonary endarterectomy; sGC = soluble guanylyl cyclase; VKA = vitamin K antagonist; WHO = World Health Organization.

patients in this analysis. According to 2015 ESC/ERS guidelines for the diagnosis and treatment of PH,[23] the 6MWD, which is affected by sex, old age, high BMI, and comorbidities reported by Mahmoud et al,[24] and BNP are variables to be assessed the prognosis of PH. The level of BNP is used to assess patient's stability. When BNP is higher than 300 mg/L, it indicates that the patient with PAH is unstable and deteriorating.[8,23] Thus, high BMI (≥30), older age (≥65), and elevated BNP (>300 mg/L)

are the risk factors associated with prognosis of PH and death. However, the above factors have no difference statistically in the outcome of all-cause death and CTEPH death in this analysis as Figs. 3 and 4 show. Based on these results, PEA and BPA should be considered early in patients with CTEPH who are candidates for intervention.

4.3. Study strengths and limitations

To the best of our knowledge, this is the first multicenter study, involving centers across our entire country. The enrolled patients underwent multiple diagnostic tests and examinations to confirm their diagnoses. This approach allows for a broader and more comprehensive representation of the population. Furthermore, the hemodynamics of patients with CTEPH were recorded completely, and the relationship between the outcome of the intervention and the volume of hemodynamics was estimated. Moreover, our findings are compatible with various international studies. The alignment with global research not only confirms our results but also positions our study as part of a larger body of evidence supporting the conclusions drawn. Finally, our study is able to be a foundation in this field in Taiwan for further research.

The present study has some limitations. First, randomization could not be provided in this prospective case-control study because the patients were assigned to receive a specific treatment. The in-operable patients could not be randomly allocated to the intervention group. A randomized trial should be performed in the future to confirm our findings. Second, statistically significant differences in patient's characteristics were between the two groups, including the average age and number of patients with severe WHO functional classification. Cox proportional hazards regression was used to correct for these variants. Therefore, the results of this study can be trusted, although a few factors differed between the two groups.

In conclusion, evidence of the impact of PEA and BPA on long-term outcomes in patients with CTEPH in the Han-Chinese population was demonstrated in this multicenter study. Patients with CTEPH receiving PEA or BPA had lower mortality rates than those not receiving PEA and BPA. PEA and BPA are significant variants that provide good long-term outcomes in patients with CTEPH.

ACKNOWLEDGMENTS

This study was supported by grants from the Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, that is, grant numbers KSVGH111-007, KSVGH110-077, VGHKS109-132, VAC110-001-4 and the Ministry of Science and Technology (grant numbers: MOST107-2314-B-075B-008-MY2 and MOST 108-2314-B-075B-007-MY2).

REFERENCES

1. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019;53:1801915.
2. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2011;183:1605–13.
3. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger R, Brida M, et al; ESC/ERS Scientific Document Group. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: developed by the 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 the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *Eur Heart J* 2022;43:3618–731.
4. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: result from an International Prospective Registry. *Circulation* 2016;133:859–71.
5. Shimura N, Kataoka M, Inami T, Yanagisawa R, Ishiguro H, Kawakami T, et al. Additional percutaneous transluminal pulmonary angioplasty for residual or recurrent pulmonary hypertension after pulmonary endarterectomy. *Int J Cardiol* 2015;183:138–42.
6. Inami T, Kataoka M, Yanagisawa R, Ishiguro H, Shimura N, Fukuda K, et al. Long-term outcomes after percutaneous transluminal pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *Circulation* 2016;134:2030–2.
7. Delcroix M, Torbicki A, Gopalan D, Sitbon O, Klok FA, Lang I, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2021;57:2002828.
8. Huang WC, Hsu CP, Sung SH, Ho WJ, Chu CY, Chang CP, et al. TSOC pulmonary hypertension committee. 2018 TSOC guideline focused update on diagnosis and treatment of pulmonary arterial hypertension. *J Formos Med Assoc* 2019;118:1584–609.
9. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011;124:1973–81.
10. Liu HY, Lu TP, Tao CW, Wu YJ, Huang WC, Hsu CH, et al. Incidence of chronic thromboembolic pulmonary hypertension in Taiwan. *J Formos Med Assoc* 2021;120:1740–8.
11. Nakamura M, Okada O, Sakuma M, Nakanishi N, Miyahara Y, Yamada B, et al. Incidence and clinical characteristics of chromic pulmonary thromboembolism in Japan compared with acute pulmonary thromboembolism: results of a multicenter registry of the Japanese society of pulmonary embolism research. *Circ J* 2002;66:257–60.
12. Taniguchi Y, Jais X, Jevnikar M, Boucly A, Weatherald J, Brenot P, et al. Predictors of survival in patients with not-operated chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant* 2019;38:833–42.
13. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2008;177:1122–7.
14. Dardi F, Manes A, Guarino D, Suarez SM, Loforte A, Rotunno M, et al. Long-term outcomes after pulmonary endarterectomy. *Ann Cardiothorac Surg* 2022;11:172–4.
15. Mayer E, Jenkins D, Lindner J, D'Armini A, Kloek J, Meyns B, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *J Thorac Cardiovasc Surg* 2011;141:702–10.
16. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the UK national cohort. *Circulation* 2016;133:1761–71.
17. Saouti N, Morshuis WJ, Heijmen RH, Snijder RJ. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a single institution experience. *Eur J Cardiothorac Surg* 2009;35:947–52.
18. Mayer E, Klepetko W. Techniques and outcomes of pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *Proc Am Thorac Soc* 2006;3:589–93.
19. FuKui S, Ogo T, Morita Y, Tsuji A, Tateishi E, Ozaki J, et al. Right ventricular reverse remodelling after balloon pulmonary angioplasty. *Eur Respir J* 2014;43:1394–402.
20. Hoole SP, Coghlan JG, Cannon JE, Taboada D, Toshner M, Sheares K, et al. Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: the UK experience. *Open Heart* 2020;7:e001144.
21. 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;5:748–55.
22. Kataoka M, Inami T, Hayashida K, Shimura N, Ishiguro H, Abe T, et al. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2012;5:756–62.
23. Nazzareno G, Marc H, Jean-Luc V, Simon G, Irene L, Adam T, et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015;2015:903–75.
24. Mahmoud A, Carel W, Neil D. Morbidity and mortality associated with obesity. *Ann Transl Med* 2017;5:161.